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Summary

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Editorial

Prezados Colegas,

Este número do nosso jornal encerra de forma oficial um ciclo de seis anos deste Editor na coordenação do nosso periódico. Um tempo de grande aprendizado pessoal e gratificante interação com colegas de todo o país. Em 2006, durante o Congresso da Sociedade Americana de Epilepsia, em Washington, recebi com grande honra a missão de capitanear nosso periódico das hábeis mãos de nosso colega Dr. Fernando Cendes, à época Editor responsável. Curiosamente é ao próprio Dr. Fernando o retorno da atribuição, desta feita em compartilhamento com o Dr. João Pereira Leite, compondo sem dúvida alguma a melhor proposta para a delineamento editorial de nosso jornal. Aos novos editores nossas boas vindas e apoio irrestrito. Sucesso!

Luciano De Paola
Editor, JECN

Message of the President of the Brazilian League of Epilepsy

Caros associados,

Estamos nos aproximando do final da nossa gestão na Diretoria Executiva da LBE. Esta deverá ser, portanto, a minha última mensagem como Presidente da LBE para o JECN. Agradeço a todos pelo apoio recebido durante estes dois anos e assim desejo sucesso para a Nova Diretoria que será eleita na Assembleia Geral da LBE, durante o 34º Congresso Brasileiro de Epilepsia e Reunião Anual da SBNC, em Ribeirão Preto, de 06 a 09 de junho deste ano. Convido a todos a visitarem a página <www.epilepsiabrasil2012.org> e participarem conosco deste importante evento da epileptologia brasileira.

Sinto-me honrado pela oportunidade de ser Presidente da LBE. Deixarei o cargo dizendo que estarei disponível para honrar o nome da nossa associação e contribuir para o sucesso da Nova Diretoria. Agradeço à Dra. Vera Cristina Terra, ao Dr. Fulvio Alexandre Scorza e à Dra. Carmen Lisa Jorge pela nossa gestão, sempre com a intenção de realizar a missão da LBE. Agradeço também ao Dr. Luciano De Paola e a Sra. Nurma Ramos Pereira pelos seus valiosos trabalhos junto ao JECN. Agradeço a todos os associados e comissões da LBE pelos seus trabalhos.

Continuemos nossos trabalhos em favor das pessoas com epilepsia e de seus familiares.

Atenciosamente,

Veriano Alexandre Jr
Presidente da Liga Brasileira de Epilepsia
Gestão 2010-2012

Journal of Epilepsy and Clinical Neurophysiology

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Epilepsy and Electroencephalographic Features. Comparative Study of Down Syndrome and Non-Syndromic Mental Retardation

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ABSTRACT

Introduction: Down syndrome (DS) is the most common chromosomal abnormality causing mental retardation and its association with epilepsy is highly variable in childhood. Although the first descriptions of the syndrome did not report seizures, their association with epilepsy is relatively common. **Methods:** were evaluated 68 individuals with DS and 83 with non-syndromic mental retardation (N-SMR). All patients underwent digital EEG, lasting at least 30 minutes and electrodes positioned according to the International 10-20 System of Electrode Placement. Data were analyzed using descriptive statistics and proportions were compared with Student's t-test and test of Differences between Proportions with $p<0.05$ considered statistically significant. **Results:** DS: 27.9% had epilepsy (first seizure with 2.2±3.7 years). Fifteen (22.1%) patients had epileptiform discharges, 5 (7.4%) hypsarrhythmia, 5 (7.4%) focal pattern, 3 (4.4%) generalized pattern and 2 (2.9%) multifocal pattern. N-SMR: 33.7% patients had epilepsy (first seizure with 1.2±4.5 years). Twenty-three (27.7%) patients had epileptiform discharges, 10 (12.0%) focal pattern, 5 (6.0%) generalized pattern and 8 (9.6%) multifocal pattern. **Conclusion:** The difference between the occurrence of epilepsy in DS and N-SMR was not statistically significant, as well as between normal EEG, EEGs with focal pattern, generalized pattern and multifocal pattern. In SD group 7.4% have shown hypsarrhythmia.The comparison with N-SMR was not possible because none of these has shown this EEG abnormality.

Keywords: Epilepsy; Down syndrome; mental retardation.

RESUMO

Epilepsia e aspectos eletrencefalográficos. Estudo comparativo entre síndrome de Down e deficiência mental não sindrômica

Introdução: síndrome de Down (SD) é a anormalidade cromossômica que mais comumente causa deficiência mental e sua associação com epilepsia é muito variável na infância. Embora as descrições iniciais da síndrome não relatassem crises, sua associação com epilepsia é relativamente comum. **Métodos:** foram avaliados 68 indivíduos com SD e 83 com retardo mental não sindrômico (RMNS). Todos os pacientes foram submetidos à EEG digital, com duração mínima de 30 minutos e com eletrodos posicionados segundo o sistema internacional 10-20 de posicionamento de eletrodos. Dados foram analisados usando estatística descritiva e proporções foram comparadas com o teste t de Student e teste de Diferença entre Proporções com $p<0,05$ sendo considerado estatisticamente significativo. **Resultados:** SD: 27,9% tinham epilepsia (primeira crise 2,2±3,7 anos). Quinze (22,1%) pacientes tinham descargas, 5 (7,4%) hipsarritmia, 5 (7,4%) padrão focal, 3 (4,4%) padrão generalizado, 2 (2,9%) padrão multifocal. N-SMR: 33,7% pacientes tinham epilepsia (primeira crise com 1,2±4,5 anos). Vinte e três (27,7%) pacientes tinham descargas, 10 (12,0%) padrão focal, 5 (6,0%) padrão generalizado e 8 (9,6%) padrão multifocal. **Conclusões:** a diferença entre a ocorrência de epilepsia no grupo SD e RMNS não foi estatisticamente significativa, assim como o EEG normal, com padrão focal, generalizado e multifocal. No grupo SD, 7,4% apresentaram hipsarritmia. A comparação com o grupo RMNS não foi possível por que ninguém neste grupo apresentou esta anormalidade no EEG.

Unitermos: Epilepsia; síndrome de Down; deficiência mental.

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INTRODUCTION

Down syndrome (DS) is the most common chromosomal abnormality cause of mental retardation, with an incidence varies according to maternal age between 1/40-1000 live births. Risk factors include advancing maternal age (because older eggs have a greater risk of improper chromosome division), parents carry the genetic translocation for DS, and having had a child with the syndrome.[1]

In 1959, with the advent of karyotype tests, the etiology of DS was determined as the presence of an abnormal extra chromosome 21. If an egg or sperm carrying 24 chromosomes combines with an egg or sperm carrying 23 chromosomes, the result would be a children with cells in which there are 47 chromosomes. This is known a genetic trisomy and almost all cases are caused by non disjunction mechanism causing trisomy 21, although unbalanced translocation involving chromosome 21 and another chromosome may occur. Rarely, less than 1% of the cases, the change in the distribution of chromosomes in the cell division occur shortly after fertilization. In these cases, the individual display cells with a combination of different patterns of chromosomes. This condition is called genetic mosaicism.[1-3]

DS is clinically characterized by mental retardation, dysmorphic facial features like slanting palpebral fissures, epicanthal folds, broaden the base of the nose, small ears, absence of the central fissure of the tongue and gray spots around the iris, particularly in neonates. Often occurs growth retardation, developmental delay, hypotonia (floppy baby), brachycephaly, single palmar crease, clinodactyly, dysplastic or hypoplastic hips, neck lymphedema, hypogonadism, gastrointestinal and cardiac malformations, diabetes, tumors, leukemia, premature degeneration of the musculoskeletal system, atlantoaxial subluxation, thyroid abnormalities, cataracts, refractive optical defects and immune deficiency. With increased life expectancy in DS, become more frequent the psychiatric disorders such as depression and dementia. Other neuropsychiatric manifestations can also occur are disruptive behavior disorders and autism.[1,2]

In 1866, seizures are not included in original report by British physician John Langdon Haydon Down. When the syndrome was described was thought to be due to a process of degeneration of the human race. At that time, physicians and researchers were more concerned with the physical and mental aspects, and therefore, the seizures were undervalued[4]. Other older researchers as Ireland (1877), Wilmarth (1890), Comby (1903) and Herrman (1905) do not reported seizures in DS[5].

Although the seizures were considered infrequent for many years, currently we know that are significantly more prevalent in DS than the general population, and less prevalent than in non-syndromic mental retardation (N-SMR).[4]

The aim of this study is to compare the incidence of seizures and electroencephalographic abnormalities in individuals with DS and N-SMR.

METHODS

The sample consisted of 68 individuals with DS (30 females and 38 males, aged 7.4±5.7 years) and 83 with N-SMR (37 female and 46 males, aged 9,4±4,8 years), all from special education programs in Brazil. Data were collected between January 2006 and December 2011. All subjects were evaluated clinically by the same physician and, where possible, underwent standardized psychometric tests. In specialized educational institutions, all participants were also evaluated by a psychologist, phonoaudiologist and occupational therapist.

In the DS group, 56 (82.4%) patients had genetic diagnosis (trisomy of chromosome 21) and all had physical characteristics that allowed the clinical diagnosis.

All patients underwent EEG in equipment Neuropmap EEG-40i, Neurofax Nihon Kohden EEG-1200 or EEG Brain Wave II, lasting at least 30 minutes and electrodes positioned according to the International 10-20 System of Electrode Placement.

To standardize the research, the terms "epilepsy" and "mental retardation" have been previously defined. Epilepsy was defined as the presence of at least one seizure, caused by a brain disorder caused by an enduring predisposition of the brain to generate recurrent seizures and their neurobiological, cognitive and psychosocial consequences.[6] Mental retardation was defined as a neurobiological disorder, characterized by significantly subaverage intellectual functioning and impairments in at least two of the following areas: communication, self-care, activities of daily living, social/interpersonal skills, and use of community resources, self direction, functional academic skills, work, leisure, health and safety.[7]

For the systematic analysis of EEG abnormalities, was considered: (a) focal pattern – up to three independent and well-delineated epileptogenic focus; (b) multifocal pattern – more than three independent epileptogenic focus; (c) generalized pattern – synchronous discharges in large areas of two hemispheres brain and (d) hypsarrhythmia. Paroxysms epileptogenic were classified as: sharp wave discharges, spike, spike-wave, polyspike and polyspike-wave. Hypsarrhythmia consists of "random high-voltage slow waves and spikes that vary from moment to moment, 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"[8].

Data were analyzed using descriptive statistics and proportions were compared with Student's t-test and test of Differences between Proportions with $p<0.05$ considered statistically significant. All data are reported as means ± SDs (standard deviations).

All aspects of this research project were approved by the Ethics Committee on Research Involving Human Subjects at our institution (number registration – 1065-12).

RESULTS

Individuals withDS

Sample of 68 individuals, 19 (27.9%) had epilepsy, and the mean age at first seizure of 2.2±3.7 years. In 15 (22.1%) patients were identified epileptiform discharges (Table 1). Five patients (7.4%) had hypsarrhythmia, 5 (7.4%) focal pattern, 3 (4.4%) generalized pattern and 2 (2.9%) multifocal pattern.

Table 1. Electroencephalographic abnormalities in patients with Down syndrome

Patients	Age	Gender	Firstseizure	Electroencephalogram
1	0,2	male	0,1	Sharp wave frontal – right
4	0,5	female	0,4	Hypsarrhythmia
5	0,6	male	0,3	Hypsarrhythmia
6	0,6	female	0,5	Hypsarrhythmia
9	0,9	female	0,6	Hypsarrhythmia
10	1,0	female	0,4	Hypsarrhythmia
15	1,4	female	1,2	Sharp wave parietal/ occipital left
28	4,7	female	4,0	Generalized spike/ polyspike
40	8,2	male	5,0	Sharp wave parietal/ occipital right
41	8,6	female	4,0	Generalized spike/ polyspike wave
50	12,4	female	2,0	Sharp wave temporal/ frontal right
57	15,0	male	0,5	Multifocal sharpwave
59	15,2	female	0,8	Multifocal sharpwave
61	15,7	female	3,3	Sharp wave frontal left/ central right
67	16,7	male	9,2	Generalized spike/ polyspike wave

Note: age and first seizure in years.

Individuals with N-SMR

Sample of 83 patients, 28 (33.7%) patients had epilepsy, and the mean age at first seizure of 1.2±4.5 years. In 23 (27.7%) patients were identified epileptiform discharges (Table 2). Ten patients (12.0%) had focal pattern, 5 (6.0%) generalized pattern and 8 (9.6%) multifocal pattern.

Table 2. Electroencephalographic abnormalities in patients with N-SMR

Patients	Age	Gender	Firstseizure	Electroencephalogram
2	1,0	male	0,2	Multifocal sharpwave
7	2,2	female	0,3	Sharp wave frontal/central right and left
8	2,3	male	0,5	Multifocal sharpwave
9	2,9	male	0,5	Generalizedspike/ spikewave
10	3,1	male	0,5	Sharp wave temporal right and left
12	3,3	female	0,8	Generalized Spike/Spike wave/polyspike
16	4,4	male	1,0	Multifocal sharpwave
17	4,6	female	1,0	Sharp wave frontal right and frontal/central left
20	5,2	female	1,2	Sharp wave occipital right and parietal left
21	5,4	male	2,0	Generalized spike/spike wave/polyspike wave
26	6,5	female	0,5	Multifocal sharpwave
27	6,6	female	3,0	Multifocal sharpwave
28	6,8	female	1,0	Sharp wave central left and temporal right
36	8,2	female	–	Sharp wave frontal/central right
41	9,0	male	0,2	Sharp wave central left and occipital right
43	9,4	female	1,5	Multifocal sharpwave
48	10,8	male	0,8	Sharp wave frontal left and frontal/central right
49	10,9	male	0,8	Multifocal sharpwave
53	11,6	male	5,0	Multifocal sharpwave
54	12,1	female	0,3	Sharp wave frontal left and parietal right
59	12,9	male	–	Sharp wave frontal/central right
64	14,1	female	–	Generalized spike wave/ polyspike wave
81	16,8	female	–	Generalized spike wave/ polyspike wave

Note: age and first seizure in years.
N-SMR – non-syndromic mental retardation.

Statistical comparison between groups

Patients with N-SMR presented the first seizure earlier than those with DS, although this difference was not significant ($p=0.08$).The difference between the occurrence of epilepsy in DS and N-SMR was not statistically significant ($p=0.44$), as well as between normal EEG ($p=1.00$), with focal pattern ($p=0.47$), generalized pattern ($p=0.66$) and multifocal pattern ($p=0.10$). Although the group with SD five patients (7.4%) have shown hypsarrhythmia in EEG, the comparison with N-SMR was not possible because none of these has shown this EEG abnormality (Table 3).

Table 3. Statistical comparison between Down syndrome and N-SMR

Patients	SD	N-SMR	*p*
Epilepsy	27.9%	33.7%	0.44
Normal EEG	26.5%	26,5%	1.00
Focal pattern	7.4%	12.0%	0.47
Generalized pattern	4.4%	6.0%	0.66
Multifocal pattern	2.9%	8.4%	0.10
Hypsarrhythmia	7.4%	0.0%	*

N-SMR – non-syndromic mental retardation.
* Statistical test is not applicable.

DISCUSSION

The incidence of seizures in DS is contradictory, varying between 1-17%.[8,9] There are distinct peaks to the incidence of seizures. In the perinatal period seizures often occur because systemic complications, cardiovascular malformations and infectionsrelated to immunodeficiency. After the first six months of life, predominate infantile spasms (West syndrome – WS), and after the fourth decade of life crises are mainly related to Alzheimer's dementia.[11] The prevalence of epilepsy increased with age, reaching 46% after the fifth decade of life[4].

Although there are many researches about the electroencephalographic abnormalities in this syndrome, no specific pattern was determined. There is a large variation in EEG of these patients, as the slowing of background activity, nonspecific burst of slow waves and epileptiform discharges with various morphologies.Even in individuals with DS without epilepsy, epileptiform discharges are common.[1-4,10]

The highest incidence of seizures has been classically attributed to changes in brain structure, although other clinical conditions such as heart defects, thyroid disease and dementia are also involved. Potential mechanisms to explain this increased frequency of seizure would be decrease neuronal density, abnormal neuronal lamination, dendritic spine dysgenesis, primitive synaptic profiles, fewer GABAergic interneurons in cortical layers II and IV, decrease voltage threshold for spike generation, abnormal potassium, calcium or sodium current, altered neurotransmitter systems GABAergic, serotoninergic, adrenergic, cholinergic or glutaminergic.[11] Ross et al.[12] compared the brain histological aspects of two patients (6-year-old DS girl and 25-year-old DS man) with normal controls, and showedcytoarchitetonic abnormalities characterized by significant poverty of granular cells in the DS brains, particularly in granular fields such as areas 3, 17 and 41.

In 1972, Morre[13] conducted a very important multi-center study involving 22 medical institutions responsible for treating patients with mental disabilities. This study evaluated 24,257 patients, 2748 with DS. The incidence of epilepsy in individuals with mental retardation without DS was 31%, and those with SD were 5.2%. In a classic paper, Seppäläinen and Kivalo.[14] analyzed the electrographic patterns in a large group of patients with SD (8.7% with epilepsy), found electrographic abnormalities in only 12% of cases and interictal paroxysmal activity in 21%. In our patients with DS, the incidence of epilepsy (27.9%) was significantly higher thanto describe by Morre (5.2%)[13] and Seppäläinen and Kivalo (8.7%).[14] However, the incidence of epilepsy in individuals N-SMR (33.7%) was very similar (31%) as described by Morre.[13] In our research, the occurrence of interictal paroxysmal activity in DS (22.1%) was resembles to report by Seppäläinen and Kivalo.[14]

The prevalence of reflex epilepsy appears to be higher in patients with DS than individuals with other forms of mental disability and the mentally healthy general population. Guerrini et al.[15] in a retrospective study of 30 SD patients with epilepsy, reported6 (20%) with reflex epilepsy (three had Lennox-Gastaut syndrome, one had benign myoclonic epilepsy of infancy, one had reflex epilepsy and partial symptomatic epilepsy and one had generalized symptomatic epilepsy). The high incidence of reflex epilepsy in SD may suggest impairment of inhibitory phenomena in the cerebral cortex of these patients. Neither of our 19 epileptic patients with SD had reflex epilepsy.

All types of seizures andepileptogenic interictal paroxysmscan occur in DS children, although the tonic-clonic, myoclonic and infantile spasms (West syndrome – WS) are considered the most frequent.[10,12] In our patients with DS, 7.4% had hypsarrhythmia, 7.4% focal pattern, 4.4% generalized pattern and 2.9% multifocal pattern. In N-SMR group, 12.0% had focal pattern, 6.0% generalized pattern and 9.6% multifocal pattern.

When we compared the incidence of epilepsy, age at first seizure, occurrence of focal, generalized or multifocal patterns, did not find statistically significant differences between DS and N-SMR groups. The clinical and electroencephalographic aspects have no consistent differences between individuals with DS and with N-SMR, except for the elevated incidence of WS in patients with DS. When we compared WS/hypsarrhythmia in EEG, observed incidence of 7.4% on DS group and none in SMR-N group.

The relationship between DS and WS is not a clinic coincidence. WS is the most frequent epileptic syndrome in DS, occurring in 0.6-13% of patients.[16] Although the characteristics of this epileptic encephalopathy are similar between patients with or without DS, children with DS appear to have better control of seizuresand evolving with the earlier disappearance of hypsarrhythmia.[16] WS can also be associated with mosaic DS.[17]

Silva et al.[18] reported 14 children with DS and WS, and no cardiac abnormalities or history of perinatal asphyxia. In this sample, the spasms started between 4 and 18 months (mean age of 8 months) and all patients had symmetrical hypsarrhythmia in EEG. Seven children exhibited other types of seizures after WS, including myoclonic seizures, tonic-clonic, atonic and atypical absence. In the seven cases who were recorded epileptic spasms, the ictal recordings was characterized with high voltage slow waves in both hemispheres followed by fast rhythmic activity of low-voltage. Lujic et al.[19] reported 11 children at the age of 3 years to 10 years with DS and WS. In this group, the spasms began at the age of 5 to 10.5 months in 10 children, in one patient at the age of 16 months. All children had their spasms controlled with ACTH and hypsarrhythmia also disappeared in all cases after drug therapy.

In children without DS, the incidence of WS is estimated between 0.25 to 0.60 cases per 1000 live births, with prevalence between 0.15 and 0.20 cases per 1000 children.[20] Therefore, although the WS is a frequentepileptic encephalopathy of childhood, it is considerably more common in children with DS than without DS.

Atypical or modified hypsarrhythmia have been reported in children with WS. However, the classic hypsarrhythmia pattern ("… random high-voltage slow waves and spikes that vary from moment to moment, 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 spikes becomes generalized, but in never appears as a rhythmically repetitive and highly organized patter; the abnormality is almost continuous…")[21] was observed in all patients with DS and WS in our research.

It is very important to know the comorbidities and complications related to this syndrome. Children with DS presenting seizures may have worse neurological outcome. To know the clinical aspects of seizures and electroencephalographic features provides a more accurate and earlier diagnosis.

REFERENCES

1. Pueschel SM. Clinical aspects of Down syndrome from infancy to adulthood. AJMG 1990;37(S7):52-6.
2. RoizenNJ, Patterson D. Down's syndrome. The Lancet 2003;361 (9365):1281-9.
3. Lejeune J. 1959. Le Mongolism. Premier exempled'aberration autosomique humaine. Ann Genet 1:41-49.
4. McVicker RW, Shanks OEP, McClelland RJ. Prevalence and associated features of epilepsy in adults with Down's syndrome. Br J Psychiatry 1994;164:528-32.
5. MacGillivray RC. Epilepsy in Down anomaly. J ment Def Res 1967;11(1):43-8.
6. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy and the International Bureau for Epilepsy. Epilepsia 2005;46(4):470-2.
7. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 4ª ed. Washington, DC: American Psychiatric Association, 1994.
8. Gibbs FA, Gibbs EL. Atlas of electroencephalography. Vol. 2: Epilepsy. Reading: Addison-Wesley; 1925.
9. Kirman BH. Epilepsy in mongolism. Archives of Disease in Childhood 1951; 26: 501-3.
10. Johannsen P. Christensen JE, Goldstein H, Nielsen VK, Mai J. Epilepsy in Down syndrome prevalence in three age groups. Seizure 1996;5:121-5.
11. Stafstrom CE. Epilepsy in Down syndrome: clinical aspects and possible mechanisms. American Journalon Mental Retardation 1993; 98: 12-26.
12. Ross MJ, Galaburda AM, Kemper TL. Down syndrome: Is there a decreased population of neurons? Neurology 1984; 34: 909-16.
13. Moore BC. Some characteristics of institutionalisedmongols. J ment Defic Res 1973;17:46-51.
14. Seppäläinen AM, Kivalo E. EEG findings and epilepsy in Down's syndrome. J MentDefic Res 1973;11(2):116-25.
15. Guerrini R, Genton P, Michelle B, Dravet C, Roger J. Reflex seizures are frequent in patients with Down syndrome and epilepsy. Epilepsia 1990;31(4):406-17.
16. Arya R, Kabra M, Gulati S. Epilepsy in children with Down syndrome. Epileptic Disord 2011;13(1):1-7.
17. Kajimoto M, Ichiyama T, Akashi A, Suenaga N, Matsufuji H, Furukawa S. West syndrome associated with mosaic Down syndrome. Brain Dev 2007;29(7):447-9.
18. Silva ML, Cieuta C, Guerrini R, Plouin P, Livet MO, Dulac O. Early clinical and EEG features on infantile spasms in Down syndrome. Epilepsia 1996;37(10):977-82.
19. Lujic L, Bosnjak VM, Delin S, Duranovic V, Krakar G. Infantile spasms in children with Down syndrome. CollAntropol 2011;35(1):213-8.
20. Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, Baram TZ, Duchowny M, Hirtz D, Pellock JM, Shields WD, Shinnar S, Wyllie E, Snead OC. Practice parameter: medical treatment of infantile spasms. Report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004; 62:1668-81.
21. Gibbs FA, Gibbs EL. Atlas of electroencephalography. Vol. 2: Epilepsy. Reading: Addison-Wesley; 1952.

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Challenges in the Surgical Treatment of Epilepsy: Hypothalamic Hamartoma in Infancy – Case report

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ABSTRACT

Introduction: Hypothalamic hamartoma is a rare congenital malformation, characterized by epilepsy, especially gelastic seizures, psychomotor developmental delay, mental retardation, behavioral disorders and precocious puberty. Epilepsy has early onset and is usually medically refractory. Etiology and pathophysiological mechanisms are unclear. The EEG can present disorganization and slowing of background activity and multifocal and/or generalized epileptogenic discharges. **Objective:** To report the difficulties and challenges of neurosurgical treatment of a hypothalamic hamartoma in an infant. **Case report:** Infant with seizures since eight months old of age. The neurological investigation revealed a lesion in tuber cinereum suggestive of hamartoma. The epilepsy evolved with resistance to antiepileptic drugs, requiring neurosurgical procedure. The endoscopic resection could not be performed because the hamartoma was firmly attached to the hypothalamus. Currently, the child remains with tonic, clonic and atonic seizures. **Discussion:** Lesionectomy performed by microsurgery or radiosurgery seems to be the most effective treatment for seizure control in patients with hypothalamic hamartomas who do not respond to clinical treatment. Callosotomy may be effective in selected cases, and lobectomy/cortical resections are not related to seizure control. In some patients, particularly in infants, lesionectomy and radiosurgery may be technically unfeasible.

Keywords: Hypothalamic hamartoma; gelastic seizures; epilepsy.

RESUMO

Desafios no tratamento cirúrgico das epilepsias: hamartoma hipotalâmico na infância – relato de caso

Introdução: hamartoma hipotalâmico é uma malformação congênita rara, que pode se manifestar através de crises epilépticas, principalmente as gelásticas, atraso do desenvolvimento neuropsicomotor, retardo mental, distúrbios comportamentais e puberdade precoce. As crises têm início precoce e são clinicamente refratárias. A etiologia e os mecanismos fisiopatogênicos não são totalmente conhecidos. O eletrencefalograma pode apresentar desde desorganização e alentecimento da atividade de base até paroxismos epileptogênicos multifocais e/ou generalizados. **Objetivo:** relatar as dificuldades e desafios do tratamento neurocirúrgico em um caso de hamartoma hipotalâmico em um lactente. **Relato do caso:** lactente com crises epilépticas desde oito meses de idade. A investigação revelou a presença de uma lesão em túber cinerium sugestiva de hamartoma. As crises tornaram-se refratárias, sendo indicado procedimento cirúrgico. A ressecção endoscópica não pôde ser realizada, pois o hamartoma encontrava-se totalmente aderido ao hipotálamo. Atualmente, a criança mantém crises tônicas, clônicas e atônicas. **Discussão:** a lesionectomia realizada por microcirurgia ou radiocirurgia parece ser o tratamento mais efetivo para o controle das crises em pacientes com hamartoma hipotalâmico. Calosotomia pode ser eficaz em casos selecionados e lobectomias/ressecções corticais não tem efetividade no controle das crises. Em alguns pacientes, particularmente nos lactentes, lesionectomia e radiocirurgia podem ser tecnicamente inviáveis. Quando o tratamento neurocirúrgico não é possível a epilepsia deve ser classificada como intratável.

Unitermos: hamartoma hipotalâmico; crise gelástica; epilepsia.

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INTRODUCTION

Although in most people with epilepsy it is possible to obtain satisfactory control of seizures with antiepileptic drugs in mono or polytherapy, 20 to 30% of these patients will remain with recurrent seizures despite treatment.

Hamartoma is a word of Greek origin, derived from *hamartion*, which means "failure of the body".[1] The hypothalamic hamartomas (HH) are rare congenital malformations of unknown etiology that arise between the sixth and seventh weeks of pregnancy, characterized as non-neoplastic lesions located in the tuber cinereum. The HH can cause serious neurological problems such as epileptic encephalopathy, psychomotor developmental delay, mental retardation and precocious puberty.[2,3]

Gelastic seizures are the most frequently observed seizure type in children with HH, although clonic, tonic, tonic-clonic, spasms and atypical absences may also occur. Seizures of laughter can also occur in symptomatic focal epilepsies originating in the frontal and temporal lobes and are characterized by episodes of stereotyped, paroxysmal and inappropriate laughter.[4]

Although the term "gelastic seizure" has been introduced by Daly and Mulder (1957), it Trousseau (1873) was who suggested that episodes of uncontrollable laughter could represent an epileptic phenomenon. In infants, gelastic seizures are less frequent, with predominance of seizures with axo-rhizomelic motor component.[5]

Some patients, who do not have their seizures controlled with antiepileptic drugs, may benefit from surgical procedures. Successful neurosurgical resection of HH can result in complete control of seizures, improved of behavior, motor development, language and cognitive ability.

The aim of this article is to present the diagnostic and therapeutic difficulties in a pediatric case of epileptic encephalopathy secondary to hamartoma in the tuber cinerium. The study was approved by the Ethics and Human Research Committee of Hospital Pequeno Príncipe (registration number: 921-11).

CASE REPORT

Female patient, two years and six months old, born by cesarean delivery, term (39 weeks gestational age). Pregnancy and birth occurred without clinical or surgical complications.

At eight months of age the patient began with epileptic seizures characterized by sudden vocal emission, followed by forced opening of the eyes, staring, generalized reduction of muscle tone, facial pallor, lip cyanosis, with an estimated duration of a few seconds. Initially the events were more frequent during sleep.

After the first year, seizure semiology changed, with increased muscle tone of the limbs (arms with flexed tonic posture and legs with extended tonic posture), upper deviation of the eyes, repetitive blinks, facial pallor and lip cyanosis, occurring mainly during wakefulness. The seizures remained short lasting, but occurring several times a day. At twelve months of life the psychomotor development was severely compromised. A family history of seizures or specific epileptic syndromes was not identified.

Subsidiary investigation revealed normal evoked auditory brainstem response and normal ophthalmologic examination with fundoscopy. The EEG performed at ten months of age revealed high amplitude slow waves, generalized and multifocal discharges of various morphologies (including sharp wave, spike, polispike, spike-wave and polispike-wave), fast generalized discharges (tonic pattern) and segments of hypsarrhythmia. The video-EEG (24 hours) showed several episodes of tonic seizures during sleep. Magnetic resonance imaging (MRI) revealed a solid nodular lesion, hyperintense on T2-weighted sequences, on the floor of the third ventricle, suggestive of a hamartoma of the tuber cinereum. Precocious puberty was investigated with pelvic ultrasound, X-rays of left wrist and hand, and hormone levels of FSH, LH and prolactin (all normal).

After failure of medical treatment with antiepileptic drugs (phenobarbital, sodium valproate, clonazepam and vigabatrin), the patient was referred to neurosurgical treatment. At two years and three months of age, the patient underwent endoscopic resection of the hamartoma. The surgery was unsuccessful, since the hamartoma was fully adhered to the hypothalamus.

At two years and six months, the patient has daily seizures (tonic, clonic, and atonic), and regression of the perceptual-motor development, with poor visual contact.

DISCUSSION

Hamartoma of the tuber cinereum is a relatively rare malformation of the developing central nervous system. Between 1934 and 1963 only 30 cases had been reported and about one hundred cases until the 1980s. The prevalence is estimated at 1 per 200,000 live births, with a predominance in males, without familial incidence or racial predominance. Disease gravity is highly variable, ranging from asymptomatic or oligossintomatic presentations to catastrophic neurological presentations.[1,5,6]

The exact sequence of events during the embryonic period that leads to the formation of a HH is not entirely clear. It is believed that the appearance of HH occurs between the fifth and sixth weeks gestational age.

Clinical aspects

Although gelastic seizures may occur in other circumstances, they are recognized as being strongly suggestive of a hamartoma in tuber cinereum. In the first two years of life these seizures may be uncharacteristic and may be preceded by many years other types of seizures with more exuberant motor manifestations. Some researchers believe that these ictal events that arise later may result from the classical phenomena of secondary epileptogenesis[7]. These epileptic seizures are often classified as medically refractor. Although seizures have varied clinical manifestations in infancy and childhood in patients with HH, delayed motor development and cognitive impairment are the rule.

A clinical study of patients with HH showed that all had seizures, 49% developed cognitive impairment and 31% manifested behavioral disturbances. Behavioral disorders varied in severity, including psychomotor agitation, episodes of violence, emotional instability, autistic features, obsessive and antisocial behavior.[8] On the other hand, severe behavioral disturbances reported in the literature are rarely seen in children below 2 years of age.

The hypothalamic-pituitary axis maintains anatomical and functional relationship with the limbic system. During early childhood, autonomic signs as changes in blood pressure, tachycardia, cyanosis, pallor and sweating may occur as a result of epileptic phenomena or non-epileptic phenomena. Autonomic manifestations may occur by changes in the limbic system, the adrenergic system and the hypothalamic-pituitary axis.[9] Nonspecific clinical manifestations often delay the diagnosis of hamartoma of cinerium tuber in infants.

Polymorphism of seizures (tonic, clonic, and atonic) and unsatisfactory response to antiepileptic drugs are common in patients with HH. Our patient had early onset of seizures suggesting worse neurological prognosis.

Early puberty is considered relatively common in children with hypothalamic lesions, can be defined as the appearance of secondary sexual characteristics before age eight in females and before age nine in males. Precocious puberty due to the increase in the secretion of hypothalamic gonadotropin-releasing hormone (GnRH), resulting in changing the hormonal hypothalamus-pituitary-gonads axis. The main signs of precocious puberty in girls are the appearance of the breasts, pubic and underarm hair, accelerated growth and oily skin. In boys, it is characterized by testicular growth, pubic hair, underarm odor, episodes of aggression, acne, and change of voice tone.

Although our patient has not shown signs of precocious puberty, we performed a preliminary investigation by the dosage of FSH, LH and prolactin, X-rays of hand and wrist and pelvic ultrasound which proved normal.

Electroencephalographic aspects

Interictal changes observed in epilepsy associated with HH are nonspecific and can range from slowing and disorganization of background activity to frequent discharges of high voltage and varied morphologies. The epileptogenic paroxysms may be generalized or multifocal (epileptic discharges in more than three independent cortical topographies).

The exact pathophysiological mechanisms by which these hamartomas generate interictal discharges and focal or generalized seizures themselves are not clear. A study using electrocorticography in eight patients with HH demonstrated ictal onset zone in the anterior temporal lobe in seven cases and in the frontal lobe in one case. However, surgical resection of these cortical regions did not lead to seizure control, suggesting that the presence of hamartoma maintains a close relationship with the mechanisms generating epileptic events.[10]

In our patient, the first EEG was performed about two months after the onset of seizures, showing slowing and disorganization of background activity in hemispheres, polymorphic discharges, hypsarrhythmia. Rapid generalized discharges were also identified, suggesting a poor neurological prognosis. The video-EEG performed several months later showed tonic seizures during sleep. Although the electrographic findings are nonspecific, they are compatible with epileptic encephalopathy associated with hypothalamic hamartoma.

Neuroimaging aspects

MRI is the method of choice in suspected cases, showing a solid and not calcified lesion, with rounded morphology in the topography of the tuber cinereum. The image must be hypointense on T1-weighted sequences and iso or hyperintense on T2. The presence of calcifications, cysts or variations in signal intensity suggest neoplastic tumors.[11]

The brain MRI findings in our patient were consistent and strongly suggestive of HH. In typical cases of hypothalamic hamartoma biopsy is often not performed.

Neurosurgical aspects

Probably the greatest challenge in neurosurgery patients with symptomatic epilepsies is to get access and resection of the lesion causing the least possible damage to healthy brain tissue. In epileptic patients with HH, lesionectomy performed by microsurgery or radiosurgery seems to be the most effective treatment for seizure control. Callosotomy can be effective in selected cases when there is a predominance of tonic and/or atonic seizures, while cortical resections and lobectomies have no efficacy.[12]

Surgical procedures to treat hamartomas of tuber cinereum have been made since mid-1960. In a large series published by Cascino et al.,[10] the surgical procedures involved resection of hamartoma, callosotomy, resection cortical and occipital or temporal lobectomy. The best results were observed in the resection of the lesion. Callosotomy decreased the frequency of atonic events, but did not reduce the frequency of other types of seizures. None of the patients who underwent cortical resection and/or lobectomy experienced improvement in their epilepsy.

Fohlen et al.[13] reported their surgical results in 18 patients, mean age 15 months, with medically refractory epilepsy secondary to HH, showing that when performed by experienced medical staff, conventional surgery (lesionectomy) is relatively safe and can promote complete control of seizures in nearly half the cases.

As injury to important structures during the resection of HH is relatively common, less invasive alternatives have been developed. In the late 1990s, the first case of a patient with epilepsy secondary to a hypothalamic hamartoma who underwent radiosurgery was reported, with complete control of seizures[2]. Radiosurgery uses a spatial coordinate system intended to address injuries of difficult surgical access, using a high dose of radiation with extreme precision in targets with well-located and well-defined limits. The advantage of radiosurgery over conventional radiotherapy is the smaller irradiation of adjacent normal brain tissue.[14] Cascino et al.[10] reported complete control of seizures after radiofrequency thermocoagulation in two patients and reduced frequency and intensity of seizures in three of six cases treated with implantation of a vagal stimulator system.

In our patient, during the neurosurgical procedure it was verified that the hamartoma was firmly adhered to the anatomical structures of the hypothalamus-pituitary axis, making the resection of high risk for developing severe endocrine disorders. For this reason, the decision was made to abort the neurosurgical procedure. Because of the risks and technical difficulties to perform radiosurgery in a child of young age, it was chosen not to treat the lesion by this method.

FINAL REMARKS

Around 20 to 30% of children with epilepsy will not have satisfactory control of seizures with the use of antiepileptic drugs alone. For these patients, neurosurgery represents a therapeutic option. However, particularly for younger children, technical difficulties may impair the performance of neurosurgical procedures.

REFERENCES

1. Sharma RR, Silva RR. Hamartoma of the hypothalamus and tuber cinereum: a brief review of the literature. J Postgrad Med 1987;33:1-13.
2. Arita K, Ikawa F, Kurisu K, et al. The relationship between magnetic resonance imaging findings and clinical manifestations of hypothalamic hamartoma. J Neurosurg 1999;91:212-22
3. Ng Y, Rekate HL, Prenger EC, et al. Transcallosal resection of hypothalamic hamartoma for intractable epilepsy. Epilepsia 2006; 47:1192-202.
4. Loiseau P, Cohadon F, Cohadon S. Gelastic epilepsy: a review and report of five cases. Epilepsia 1971;12:313-23.
5. Daly DD, Mulder DW. Gelastic epilepsy. Neurology 1957;7:189-92.
6. Rosenfeld, JV. The evolution of treatment for hypothalamic hamartoma: a personal odyssey. Neurosurg Focus 2011;30(2):E1.
7. Berkovic SF, Arzimanoglou A, Kuzniedky R, et al. Hypothalamic hamartoma and seizures: a treatable epileptic encephalopathy. Epilepsia 2003;44:969-73.
8. Palmini A, Chandler C, Andermann F, et al. Resection of the lesion in patients with hypothalamic hamartomas and catastrophic epilepsy. Neurology 2002;58:1338-47.
9. Gordon N. Gelastic seizures. J Pediatr Neurol 2003;1(2):69-73.
10. Cascino GD, Andermann F, Berkovic SF. Gelastic seizures and hypothalamic hamartomas: evaluation of patients undergoing chronic intracranial EEG monitoring and outcome of surgical treatment. Neurology 1993; 43:747-50.
11. Saleem, SN, Said AM, Lee DH. Lesions of the Hypothalamus: MR Imaging Diagnostic Features. RadioGraphics 2007;27:1087-108.
12. Gomes MM. Epilepsia focal refratária: perspectivas terapêuticas. Rev bras Neurol 2005;41(2):37-43.
13. Fohlen M, Lellouch A, Delaland O. Hypothalamic hamartoma with refractory epilepsy: surgical procedures and result in 18 patients. Epileptic Disord 2003;5(4):267-73.
14. Mascarenhas F, Costa MS, Ortiz M, et al. A radiocirurgia estereotáxica em tumores benignos e malignos do sistema nervoso central. Acta Med Port 2005;18:45-60.

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Different Levels of MT-I/II Between Patients With MTLE With or Without Seizure Generalization: Does Hippocampal MT-I/II Affects Seizure Spread, or Does Seizure Spread Promotes Differential Expression of MT-I/II?

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ABSTRACT

In the central nervous system, zinc is released along with glutamate during neurotransmission and, in excess, can promote neuronal death. Experimental studies have shown that metallothioneins I/II (MT-I/II), which chelate free zinc, can affect seizures and reduce neuronal death after *status epilepticus*. Our aim was to evaluate the expression of MT-I/II in the hippocampus of patients with temporal lobe epilepsy (TLE). Hippocampi from patients with pharmacoresistant mesial temporal lobe epilepsy (MTLE) were evaluated for expression of MT-I/II and for neuronal, astroglial, and microglial populations. Compared to control cases, MTLE group displayed widespread increase in MT-I/II expression, astrogliosis and reduced neuronal population. MT-I/II levels did not correlate with any clinical variables, but patients with secondary generalized seizures (SGS) had less MT-I/II than patients without SGS. In conclusion, MT-I/II expression was increased in hippocampi from MTLE patients and our data suggest that it may be associated with different seizure spread patterns.

Keywords: Metallothioneins; zinc homeostasis; gliosis; epilepsy; neuronal density.

RESUMO

Níveis diferentes de MT-I/II entre pacientes com MTLE com ou sem crise generalizada: os níveis hipocampais de MT-I/II afetam o alastramento das crises, ou o alastramento das crises promove expressão diferencial de MT-I/II?

No sistema nervoso central, o zinco é liberado juntamente com o glutamato durante a neurotransmissão e, quando liberado em excesso, pode promover morte neuronal. Estudos indicam que as metalotioneínas I/II (MT-I/II), proteínas quelantes de zinco livre, podem afetar parâmetros relacionados às crises e reduzir a morte neuronal subsequente a um *status epilepticus*. Nosso objetivo foi avaliar a expressão de MT-I/II no hipocampo de pacientes com epilepsia do lobo temporal (ELT). Hipocampos de pacientes com ELT mesial (ELTM) resistente ao tratamento farmacológico foram avaliados para a expressão de MT-I/II e para as populações neuronal e astroglial. Quando comparadas com o grupo controle, pacientes com ELTM apresentaram aumento na expressão de MT-I/II, astrogliose e redução na densidade neuronal. Não foram observadas correlações entre os níveis de MT-I/II e as características clínicas dos pacientes, mas pacientes com crises secundariamente generalizadas apresentaram um aumento menor nos níveis de MT-I/II que os pacientes sem estas crises. Em resumo, um aumento na expressão de MT-I/II é observado em pacientes com ELTM e nossos dados sugerem que o aumento pode estar associado a diferentes padrões de crises epilépticas.

Unitermos: Metalotioneínas; homeostase do zinco; gliose; epilepsia; densidade neuronal.

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INTRODUCTION

Zinc (Zn^{2+}) is an important modulator of glutamatergic transmission in the central nervous system (CNS).[1-3] Zn^{2+} is concentrated in presynaptic vesicles, along with glutamate, and released during normal neurotransmission.[4-8] Hippocampal neurons are specially rich in vesicular Zn^{2+}, particularly in the axonal boutons of granule cells, CA3 and CA1 pyramidal cells and prosubicular neurons.[5-7,9,10] In temporal lobe epilepsy (TLE), one of the most frequent drug-resistant epilepsies in adults, the hippocampus is associated with seizure generation.[11,12] The intense neuronal activity during seizures can release high amounts of Zn^{2+} in the synaptic cleft,[13,14] promoting reactive oxygen species (ROS) production,[15] which can ultimately lead to hippocampal neuronal death.[13-17] In fact, studies in hippocampi from TLE patients who underwent epilepsy surgery have shown neuronal loss,[18-20] increased glial reaction[21-24] and reorganization of mossy fibers axon collaterals into the inner molecular layer of the granule cell dendrites.[19,25] This synaptic reorganization of Zn^{2+}-enriched terminals has been hypothesized to contribute to synchronous firing and epileptiform activity.[19]

Metallothioneins (MTs) are low molecular weight, cystein-enriched proteins that bound Zn^{2+} and cadmium. They can be found in various tissues, in four isoforms.[26] Isoforms I, II and III are found in the central nervous system (CNS), where the isoforms I and II are coexpressed in astrocytes and the isoform III is expressed in neurons.[27,28] MTs participate in Zn^{2+} homeostasis, scavenging ROS in the brain[29] and stimulate the expression of several neurotrophic and antiinflamatory factors.[30] Studies on rodent models of TLE have shown that MT expression is increased in the hippocampal formation shortly after seizures[31,32] and that high levels of MTs I and II are associated with reduced neuronal death after seizure-induced damage.[32-34]

Since MT-I/II levels may be associated with neuron survival after seizures, we hypothesize that MT-I/II expression is altered in TLE and can be associated with the preservation of neuronal density in the hippocampus of TLE patients. Therefore, in this study we evaluated the immunoexpression of MT-I/II and its correlation with hippocampal neuron density in hippocampi of patients with chronic TLE.

MATERIALS AND METHODS

Patients and clinical data

Patients with drug-resistant epilepsy were evaluated at the University of São Paulo Epilepsy Surgical Centre in Ribeirão Preto (Brazil), according to standard protocols published elsewhere.[35] MTLE patients (n=69) were patients with hippocampal atrophy or with normal hippocampal volume at MRI without other lesions associated with TLE.

For comparison purposes in the neuropathology studies, autopsy controls (Ctrl, n=20) were obtained from autopsy cases without history of neurological diseases, with no sign of CNS pathologies in *post mortem* pathological evaluation, and with less than 10 hours *post mortem*.

Medical records of all evaluated patients were assessed for clinical data analysis. The clinical variables investigated were age at death and cause of death for Ctrl patients and age at surgery, epilepsy duration, age at the first recurrent seizure, seizure frequency per month, presence of secondary generalized seizures, and neuropathological evaluation for MTLE patients. This study followed the principles of the Declaration of Helsinki, was registered in Brazilian's Health Ministry and was approved by our local ethics committee (processes HCRP 9370/2003 and HCRP 2634/2008).

Tissue collection and immunohistochemistry

Hippocampi from surgery or autopsy were cut in coronal sections and placed in 10% (vol/vol) buffered formaldehyde for one week, followed by paraffin embedding. Immunohistochemistry was performed in 8μm sections at the level of hippocampal body for evaluation of neuronal and astroglial populations and for MT-I/II expression with antibodies against, respectively, NeuN, GFAP and MT-I/II. The sections were submitted to endogenous peroxidase blocking with 4.5% H_2O_2 in 50 mM phosphate-saline buffer (PSB) pH 7.4, for 15 minutes, followed by microwave antigenic retrieval in 10mM sodium citrate buffer pH 6.0 (for GFAP) or 50 mM Tris-HCl pH 9.6 (for NeuN and MT-I/II). After achieving room temperature, the sections went through blocking free aldehyde groups with Tris-glycine 0.1 M pH 7.4 for 45 minutes, followed by blocking buffer with 5% defatted milk and 15% goat serum (# S-1000, Vector) in Triton buffer (PTB, 20mM phosphate + 0.45M NaCl, pH 7.4, with 0.3% Triton X-100) for four hours. The sections were then incubated with primary antibodies in blocking buffer for 16 hours. We used primary monoclonal antibodies raised in mouse anti-human GFAP (clone 6F2, #M0761, Dako), anti-murine NeuN (clone A60, #MAB377, Chemicon) and anti-equine MT-I/II (clone E9, #M0639, Dako), diluted in blocking buffer at concentrations of 1:500. The primary antibodies were detected using biotinylated rabbit anti-murine IgG (#E0354, Dako), at 1:200 dilution in blocking buffer, for one hour, followed by revelation with avidin-biotin-peroxidase system (Vectastain Elite ABC kit, #PK6100, Vector) and diaminobenzidine as chromogen (DAB, #34001, Pierce Biotechnology). The development times in DAB solution were 10.5 minutes for NeuN and 8 minutes for MT-I/II and GFAP.

Immunohistochemistry analysis

Images of all hippocampal regions were obtained with a video monochrome charge-coupled device camera (CCD;

Hamamatsu Photonics Model 2400, Japan) attached to an Olympus microscope (Model BX60, Melville, NY), and captured, averaged, and digitized using a frame grabber (Scion Corporation, Frederick, MD) on a Macintosh computer (Model G3, Cupertino, CA). Illuminance was uniformly maintained and regularly checked using optical density standards (Kodak, Rochester, NY). After captured, the image was analyzed using image system software (ImageJ, version 1.37c).

Quantification of the immunohistochemistry was performed with threshold tool, with the investigator blind to the group allocation. After the selection of the region of interest (ROI), the software calculated the immunopositive area by counting all pixels with gray intensity equal or superior to the threshold of staining. A complete protocol for threshold tool can be found at rsbweb.nih.gov/ij/docs/examples/stained-sections/index.html. The threshold was defined for each protein evaluated, based on the mean immunopositivity of all control cases. The evaluated regions were outer molecular layer (OML), inner molecular layer (IML), granule cell layer (GCL), subgranular zone (SGZ), the hilus (HIL) and the stratus piramidale of CA4, CA3, CA2, CA1, prosubiculum (PRO) and subiculum (SUB). The characterization of hippocampal regions was based on the Lorente de Nó's classification.[36] Results were shown as percentage of immunopositive area/total area.

Additionally, neuronal density was evaluated in the NeuN stained sections. Neuronal count was processed in ImageJ 1.37c software with a 520x magnification for granule cell layer and 260x for pyramidal neurons of CA4, CA3, CA2, CA1, prosubiculum and subiculum. Neuronal densities were estimated with the correction of Abercrombie[37], which permits to estimate the neuronal density through mathematical method, and the results were shown as thousands of cells per cubic millimeter.

Statistical analysis

Statistics were carried out in SigmaStat 3.1 software. Tests for normality and homogeneity of variances were performed to define data distribution. For parametric variables, t-test was performed and, for the non-parametric variables, Mann-Whitney test was used. Correlation between MT expression and clinical variables was performed using Pearson's test. All results were considered significant at $p<0.05$.

RESULTS

Clinical data

The clinical characteristics of study participants are summarized in Table 1. Patients with MTLE and Ctrl patients have the same age ($p=0.175$). Epilepsy duration was 25±10 years, and the age at onset was 13±1. MTLE patients had seven seizures by month, being one of those a secondary generalized seizure (SGS).

Table 1. Clinical history of patients with MTLE and Ctrl cases

Group	Ctrl	MTLE
Age at evaluation* (years)	42±16	38±10
Epilepsy duration (years)	_	25±10
Age at epilepsy onset (years)	_	13±1
Minimal seizure frequency (per month)	_	7
Number of secondary generalizations (per month)	_	1
Frequency of secondary generalization (%)	_	59

* Age of death for Ctrl and age at surgery for TLE.

Immunohistochemistry evaluation

Neuronal density, estimated with the count of NeuN positive cells, was reduced in the granule cell layer, CA4, CA3, CA2, CA1, prosubiculum and subiculum of the MTLE group, when compared to Ctrl ($p < 0.03$). Increased astrogliosis was observed in all hippocampal regions of MTLE, compared to Ctrl ($p < 0.001$). MT-I/II expression, observed in astrocyte-like cells, was increased in all hippocampal subfields evaluated ($p < 0.032$). For further details, see Table 2.

Table 2. Neuronal density and percentage of immunopositive area for GFAP and MT-I/II in patients with MTLE and Ctrl

Region	NeuN*			GFAP**			MT-I/II**		
	MTLE	Ctrl	*p*	MTLE	Ctrl	*p*	MTLE	Ctrl	*p*
OML	_	_	_	59	4	<0.001	46	10	<0.001
IML				58	6	<0.001	58±31	34±30	0.003
GCL	187.5	375	<0.001	57±18	22±18	<0.001	46±26	28±26	0.008
SGZ	_	_	_	90	69	<0.001	48	11	<0.001
HIL	_	_	_	86	28	<0.001	30	7	<0.001
CA4	9.0	35.9	<0.001	72±22	18±21	<0.001	30	12	0.031
CA3	19±11	47±6	<0.001	60	6	<0.001	55±28	27±28	<0.001
CA2	29±9	41±4	<0.001	52	5	<0.001	62±25	30±29	<0.001
CA1	4.5	41.9	<0.001	87	2	<0.001	66±28	31±31	<0.001
PRO	19±8	32±3	<0.001	78	1	<0.001	64±29	34±32	<0.001
SUB	30±6	35±3	0.029	23	0.2	<0.001	66	31	<0.001

* Neuronal density, as thousands of cells per cubic millimeter.
** Percentage of immunopositive area in the amostral area.

The results are shown as median (for Mann Whitney test) or mean ± standard deviation (for Student's t-test). OML = outer molecular layer; IML = inner molecular layer; GCL = granule cell layer; SGZ = subgranule zone; HIL = hilus; PRO = prosubiculum; SUB = subiculum.

Tissue alterations and seizures

In MTLE group, patients without SGS had increased MT-I/II immunopositivity, when compared with patients with SGS, in the inner molecular layer ($p=0.037$), granule cell layer ($p=0.018$), subgranule zone ($p=0.004$), CA2 ($p=0.039$) and CA1 ($p<0.043$). A trend to increased MT-I/II immunopositivity was observed in the outer molecular layer ($p=0.072$), CA4 ($p=0.076$) and subiculum ($p=0.068$). No differences in neuronal or astroglial populations were observed between MTLE patients with or without SGS. Frequency of seizures did not correlate with NeuN, GFAP or MT-I/II in all hippocampal subfields.

DISCUSSION

In the present study, we found an increased MT-I/II expression in all hippocampal subfields of MTLE patients. In the CNS, MT-I/II are expressed mainly by astrocytes[38] and, when the tissue suffers an injury, increased MT-I/II expression is observed in astrocytes and microglias.[28,38] We also observed that higher degree of MT-I/II expression was observed in regions with higher astrogliosis. Increased glial population is a common finding in TLE[21-24] and is associated with the degree of neuronal death.[22-24,39] In our study, an increased expression of MT-I/II was observed in astrocytes and in a few neurons of some patients. Thus, our data support the notion that MT-I/II changes are essentially related to astroglial population.

Studies in rodents with kainic acid-induced SE showed an association between MT-I/II expression and neuronal protection. Transgenic mice over-expressing MT-I/II have reduced neuronal death, compared to wild type animals.[34] In addition, mice with reduced MT-I/II expression[32] or knockouts for MT-I/II[33] had increased neuronal death following SE, compared to wild type mice. In our study, however, the higher MT-I/II expression was observed in regions with lower neuronal density, indicating that MT-I/II was not associated with neuronal survival. In agreement with our data, an association between the severity of tissue damage and the increase in MT-I/II expression has been reported in mice subjected to soman-induced *status epilepticus* (SE).[31]

Data have shown that the increased MT-I/II immunoreactivity observed in animal models of TLE can also be a factor associated with the seizure generation process. Transgenic mice over-expressing MT-I, have increased seizure duration, a tendency to reduced latency, but similar number of seizures after KA administration.[34] Since MT-I/II act chelating free Zn^{2+}[14,27] and Zn^{2+} chelation increases tissue excitability and facilitates seizure generation[40], excessive MT-I/II levels can reduce free Zn^{2+} in the synaptic cleft, increasing neuronal excitability and affecting seizure generation. We found no correlation between seizure frequency and MT-I/II expression in TLE.[34]

In MTLE, we found increased levels of MT-I/II in patients without SGS, when compared with those with SGS. This could indicate that MT-I/II is associated with different seizure spread patterns from the epileptogenic hippocampus to other brain regions. It is important to point out that no difference in neurons or glial cells was observed between MTLE with and without SGS. Studies from different groups also observed no association between changes in the hippocampus and SGS.[41-43] All those observations suggest that the increased MT-I/II expression in patients without SGS is not an effect of gliosis, but it is independently associated with SGS. Further studies with animal models of TLE must evaluate more closely the relationship between MT-I/II expression and seizure susceptibility.

Some limitations of our study must be pointed out. So far, studies about MT-I/II expression in animal models of TLE only evaluated the acute period following SE. Considering that our study was performed in patients with chronic epilepsy, it is difficult to establish comparisons between human and animal data. The lack of correlation between seizure frequency and MT-I/II expression does not exclude an association between seizures and MT-I/II expression. Other seizure characteristics, such as seizure duration and time between the last seizure and the surgery, could better correlate with MT-I/II expression than isolate seizure frequency.

Finally, our study may have translational implications in the future. The role of MTs in antiinflamatory response, neurotrophic factor expression, and protection against ROS and heavy metals make those proteins interesting for clinical applications. Studies have shown that EmtinB, a syntethic peptide that mimics the actions of MTs, attenuates KA-induced seizures and protects neurons from excitotoxic death.[30] Further studies with EmtinB and MTs should be done to evaluate the role of these proteins in neuronal survival and seizure susceptibility.

In summary, our data indicate that increased MT-I/II expression is a plastic alteration of chronic TLE, primarily related to the astrogliosis, a common finding in chronic TLE. Our findings suggest that increase MT-I/II expression may contribute to the control of the brain hyperexcitability.

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REFERENCES

1. Peters S, Koh J, Choi DW. Zinc selectively blocks the action of N-methyl-D-aspartate on cortical neurons. Science 1987;236:589-93.
2. Westbrook GL, Mayer ML. Micromolar concentrations of Zn^{2+} antagonize NMDA and GABA responses of hippocampal neurons. Nature 1987;328:640-643.
3. Rassendren FA, Lory P, Pin JP, Nargeot J. Zinc has opposite effects on NMDA and non-NMDA receptors expressed in Xenopus oocytes. Neuron 1990;4:733-40.
4. Haug FMS. Electron microscopic localization of the zinc in hippocampal mossy fiber synapses by a modified sulphide silver procedure. Histochemie 1967;8:355-68.
5. Frederickson CJ, Hernandez MD, McGinty JF. Translocation of zinc may contribute to seizure-induced death of neurons. Brain Res 1989;480:317-21.
6. Perez-Clausell J. Distribution of terminal fields stained for zinc in the neocortex of the rat. J Chem Neuroanat 1996;11:99-111.
7. Frederickson CJ, Suh SW, Silva D, Frederickson CJ, Thompson RB. Importance of zinc in the central nervous system: the zinc-containing neuron. J Nutr 2000;130:1471S-83S.
8. Brown CE, Dyck RH.Distribution of zincergic neurons in the mouse forebrain. J Comp Neurol 2004;479:156-67.
9. Takeda A, Itoh H, Tamano H, Oku N. Responsiveness to kainate in young rats after 2-week zinc deprivation. Biometals 2006;19:565-72.
10. Amaral D, Lavenex P. Hippocampal Neuroanatomy. The Hippocampus Book. 1ª ed. Oxford University Press; 2006. p.37-114.
11. Mathern GW, Babb TL, Leite JP, Pretorius K, Yeoman KM, Kuhlman PA. The pathogenic and progressive features of chronic human hippocampal epilepsy. Epilepsy Res 1996;26:151-61.
12. Pitkanen A. Efficacy of current antiepileptics to prevent neurodegeneration in epilepsy models. Epilepsy Res 2002;50:141-60.
13. Weiss JH, Sensi SL, Koh JY. $Zn^{(2+)}$: a novel ionic mediator of neural injury in brain disease. Trends Pharmacol Sci 2000;21:395-401.
14. Colvin RA, Fontaine CP, Laskowski M, Thomas D. Zn^{2+} transporters and Zn2+ homeostasis in neurons. Eur J Pharmacol 2003;479:171-85.
15. Kim EY, Koh JY, Kim YH, Sohn S, Joe E, Gwag BJ. Zn^{2+} entry produces oxidative neuronal necrosis in cortical cell cultures. Eur J Neurosci 1999;11:327-34.
16. Treiber C. Metals on the brain.Sci Aging Knowledge Environ 2005;2005:e27.
17. Frederickson CJ, Koh JY, Bush AI. The neurobiology of zinc in health and disease. Nat Rev Neurosci 2005;6:449-62.
18. Babb TL, Brown WJ, Pretorius J, Davenport C, Lieb JP, Crandall PH. Temporal lobe volumetric cell densities in temporal lobe epilepsy. Epilepsia 1984;25:729-40.
19. Babb TL, Kupfer WR, Pretorius JK, Crandall PH, Levesque MF. Synaptic reorganization by mossy fibers in human epileptic fascia dentata. Neuroscience 1991;42:351-63.
20. Mathern GW, Leite JP, Babb TL, Pretorius JK, Kuhlman PA, Mendoza D et al. Aberrant hippocampal mossy fiber sprouting correlates with greater NMDAR2 receptor staining. Neuroreport 1996;7: 1029-35.
21. Salanova V, Markand O, Worth R, Garg B, Patel H, Asconape J et al. Presurgical evaluation and surgical outcome of temporal lobe epilepsy. Pediatr Neurol 1999;20:179-84.
22. Proper EA, Jansen GH, van Veelen CW, van Rijen PC, Gispen WH, de Graan PN. A grading system for hippocampal sclerosis based on the degree of hippocampal mossy fiber sprouting. ActaNeuropathol (Berl) 2001;101:405-9.
23. Swartz BE, Houser CR, Tomiyasu U, Walsh GO, DeSalles A, Rich JR et al. Hippocampal cell loss in posttraumatic human epilepsy. Epilepsia 2006;47:1373-82.
24. Prayson RA, Yoder BJ. Clinicopathologic findings in mesial temporal sclerosis treated with gamma knife radiotherapy. Ann Diagn Pathol 2007;11:22-26.
25. Sutula T, Cascino G, Cavazos J, Parada I, Ramirez L. Mossy fiber synaptic reorganization in the epileptic human temporal lobe. Ann Neurol 1989;26:321-30.
26. Kille P, Hemmings A, Lunney EA. Memories of metallothioneis. Biochim Biophys Acta 1994;1205:151-61.
27. Aschner M, Cherian MG, Klaassen CD, Palmiter RD, Erickson JC, Bush AI. Metallothioneins in brain – the role in physiology and pathology. Toxicol Appl Pharmacol 1997;142:229-42.
28. Wiese L, Kurtzhals JA, Penkowa M. Neuronal apoptosis, metallothionein expression and proinflammatory responses during cerebral malaria in mice. Exp Neurol 2006;200:216-26.
29. Ebadi M, Brown-Borg H, El RH, Singh BB, Garrett S, Shavali S et al. Metallothionein-mediated neuroprotection in genetically engineered mouse models of Parkinson's disease. Brain Res Mol Brain Res 2005;134:67-75.
30. Sonn K, Pankratova S, Korshunova I, Zharkovsky A, Bock E, Berezin V et al. A metallothionein mimetic peptide protects neurons against kainic acid-induced excitotoxicity. J Neurosci Res 2010;88: 1074-82.
31. Pazdernik TL, Emerson MR, Cross R, Nelson SR, Samson FE. Soman-induced seizures: limbic activity, oxidative stress and neuroprotective proteins. J ApplToxicol 2001;21Suppl 1:S87-S94.
32. Penkowa M, Molinero A, Carrasco J, Hidalgo J. Interleukin-6 deficiency reduces the brain inflammatory response and increases oxidative stress and neurodegeneration after kainic acid-induced seizures. Neuroscience 2001;102:805-18.
33. Carrasco J, Penkowa M, Hadberg H, Molinero A, Hidalgo J. Enhanced seizures and hippocampal neurodegeneration following kainic acid-induced seizures in metallothionein-I + II-deficient mice. Eur J Neurosci 2000;12:2311-22.
34. Penkowa M, Florit S, Giralt M, Quintana A, Molinero A, Carrasco J et al. Metallothionein reduces central nervous system inflammation, neurodegeneration, and cell death following kainic acid-induced epileptic seizures. J Neurosci Res 2005;79:522-34.
35. Leite JP, Terra-Bustamante VC, Fernandes RM, Santos AC, Chimelli L, Sakamoto AC et al. Calcified neurocysticercotic lesions and postsurgery seizure control in temporal lobe epilepsy. Neurology 2000;55:1485-91.
36. Lorente de Nó R. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammoniac system. Journal of Psychologie und Neurologie 1934;45:113-77.
37. Abercrombie M. Estimation of nuclear population from microtome sections. Anat Rec 1946;94:239-147.
38. Hidalgo J. Metallothioneins and Brain Injury: What Transgenic Mice Tell Us. Environ Health Prev Med 2004;87-94.
39. Crespel A, Coubes P, Rousset MC, Brana C, Rougier A, Rondouin G et al. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. Brain Res 2002;952:159-69.
40. Dominguez MI, Blasco-Ibanez JM, Crespo C, Nacher J, Marques-Mari AI, Martinez-Guijarro FJ. Neural overexcitation and implication of NMDA and AMPA receptors in a mouse model of temporal lobe epilepsy implying zinc chelation. Epilepsia 2006;47:887-99.
41. Bernasconi N, Natsume J, Bernasconi A. Progression in temporal lobe epilepsy: differential atrophy in mesial temporal structures. Neurology 2005;65:223-28.
42. Szabo CA, Lancaster JL, Lee S, Xiong JH, Cook C, Mayes BN et al. MR imaging volumetry of subcortical structures and cerebellar hemispheres in temporal lobe epilepsy. AJNR Am J Neuroradiol 2006;27:2155-60.
43. O'Dwyer R, Silva Cunha JP, Vollmar C, Mauerer C, Feddersen B, Burgess RC et al. Lateralizing significance of quantitative analysis of head movements before secondary generalization of seizures of patients with temporal lobe epilepsy. Epilepsia 2007;48: 524-30.

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Pre-Surgical Mood Disorders Associated to Worse Post-Surgical Seizure Outcome in Patients with Refractory Temporal Lobe Epilepsy and Mesial Temporal Sclerosis

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SUMMARY

Objectives: This study aims at verifying the impact of pre-surgical PD on seizure outcome in patients with refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE-MTS). **Methods:** After previous consent, retrospective data from 115 surgically treated (corticoamygdalohyppocampectomy) TLE-MTS patients (65 females; 56.5%) were analyzed. Psychiatric evaluations were performed through DSM-IV criteria. Engel IA was established as a favorable prognosis. **Results:** Forty-five patients (41.6%) were classified as Engel IA, while 47 (40.8%) presented pre-surgical PD. Depression (OR=5.11; p=0.004) appeared as a risk factor associated to a non-favorable seizure outcome. **Conclusion:** In patients with refractory TLE-MTS, the presence of depression predicts an unfavorable outcome.

Keywords: Temporal lobe epilepsy; mesial temporal sclerosis; epilepsy surgery; psychiatric disorders; seizure outcome.

RESUMO

Transtornos de humor pré-cirúrgicos associados ao prognóstico pós-cirúrgico desfavorável em pacientes com epilepsia do lobo temporal e esclerose mesial temporal

Objetivo: No presente trabalho avaliamos o impacto da presença de transtorno psiquiátrico pré-cirúrgico sobre o prognóstico cirúrgico em pacientes com epilepsia do lobo temporal e esclerose mesial temporal (ELT-EMT). **Metodologia:** Analisamos, retrospectivamente, os dados de 115 pacientes com ELT-EMT (65 mulheres, 56,5%) tratados cirurgicamente (corticoamigdalohipocampectomia). As avaliações psiquiátricas foram feitas de acordo com os critérios DSM-IV. O prognóstico favorável foi definido como ausência de crises desde a cirurgia (Engel IA). **Resultados:** Dos 115 pacientes tratados, 45 (42,6%) tiveram prognóstico favorável e 47 (40,8%) apresentavam transtorno psiquiátrico pré-operatório. A presença de depressão (OR=5,11; p=0,004) foi associada ao prognóstico cirúrgico desfavorável. **Conclusão:** A presença de depressão durante a avaliação psiquiátrica pré-operatória é um fator preditivo de prognóstico desfavorável em pacientes com ELT-EMT.

Unitermos: Epilepsia do lobo temporal, esclerose mesial temporal, cirurgia de epilepsia, transtorno psiquiátrico, resultado cirúrgico.

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1 INTRODUCTION

Anterior and mesial temporal lobectomy (ATL) is an important treatment option for 30 to 40% ofpatients with temporal lobe epilepsywhich present a medically intractable disease, with an approximately 70% chance of long-term seizure freedom.[1-5] Refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE-MTS) is a condition that compromises the main structures of the limbic system,being also one of the most common surgically remediable epileptic syndromes.[1-5]

Studies have observed a comorbid psychiatric prevalence rate of 20-40% in TLE-MTS, rising to 70% in patients with refractory forms of epilepsy.[6-11] Mood disorders are the most common (24-74%), followed by anxiety (10-25%), psychotic (2-9%) and personality disorders (1-2%).[6-11] The association between pre-surgical PDand a worse post-surgical seizure outcome in patients with refractory epilepsy submitted to epilepsy surgery has been also increasingly recognized.[12-15] However,different types and etiologies of epilepsy have been analyzed together in such studies, precluding important insights regarding specific epilepsy syndromes.[16] The present study aims to verifytherisk of pre- and post-surgical PDin predisposing to a worse seizure outcome in a homogeneous series ofpatients with refractory TLE-MTS submitted to ATL.

2 METHODS

2.1 Subjects

All patients were followed-up in the Epilepsy Surgical Program of the Universidade Federal de São Paulo, Brazil, from 2003 to 2011. After previous consent, 115 TLE-MTS patients were included in the study. Inclusion criteria were patients older than 18 years of age, the presence of electroclinical diagnosis of TLE based on ILAE,[17] ATL as the surgical procedure and follow-up of at least one year. All participants hadclear MRI findings of unilateral MTS and concordant interictal and ictal EEG data.

2.2 Procedures

Patients underwent 2-6 days of continuous video-electroencephalographic(VEEG) MTS was defined if atrophy, an increased T2-weighted signal, a decreased T1-weighted signal, and disrupted internal structure of the hippocampus were present on visual inspection of MRI. Epilepsy was considered resistant to medical treatment when seizures persisted after the utilization of at least two first line medications for partial seizures at highest tolerated doses. The surgical procedure consisted of "en block" resection of superior, middle, inferior temporal and fusiform gyri, with posterior limit of 4.5 cm from the tip of the temporal lobe. After opening the temporal horn, the mesial temporal structures (hippocampus, amygdala and parahyppo-campal gyrus) were also resected "en block".[1,2,5] The most recent Engel's classification was utilized to measure the patients' seizure outcome,[18] and only the subcategory Engel IA (completely seizure-free since surgery) was considered as a favorable prognosis. Initial precipitant injury (IPI) was defined as the occurrence of severe cere-bral events in the first year of life before the appearance of epilepsy that required medical intervention and/or hospitalization. Febrile seizures, meningoencephalitis, head trauma or severe perinatal hypoxia were considered as IPI.

2.3 Psychiatric evaluation

All patients were evaluated by the same psychiatrist (GMAF) through the Diagnostical and Statistical Manual of Mental Disorders (DSM-IV) axis I criteria.[19] The presence of other specific psychiatric diagnoses of epilepsy not covered by DSM-IV, such as the interictal dysphoric disorder (IDD), postictal psychosis (PIP) and interictal psychosis (IIP) were evaluated through ILAE criteria.[20] Information about lifetime history of psychiatric treatment, defined as any treatment with psychiatric drugs occurred in the past, was collected with patients in the first clinical interview, as well as family history of epilepsy and PD. Due to ethical issues, all patients underwent pre-surgical and at least one post-surgical psychiatric evaluation within the first year after surgery. In addition to surgical follow up, those patients with pre-surgical, post-surgical and/or *de novo* PD received psychiatric follow-up after surgery, and the most recent psychiatric evaluation was considered for analysis.

2.4 Statistics

Statistical analyses were performed with SPSS 10.0 software. Patients were divided into those with or without a favorable post-surgical outcome at the moment of the study. Bivariate statistical analyses were performed through the most adequate statistical test for each situation (chi-square, χ^2, Fisher's exact test or Student's t test for unequal variances). A multivariate statistical analysis (logistic regression model) was performed to identify predictors ofa non-favorable seizure outcome, and the *odds-ratio* (OR) was calculated for significant risk factors. P value of <0.05 was considered significant.

3 RESULTS

Data from 115 TLE-MTS (65 females; 56.5%) were analyzed. The mean age and epilepsy duration were of 36.9 ± 10.77 and 27.1 ± 12.14 years, respectively. All patients had been in use of association of two or more antiepileptic drugs (AED). Carbamazepine (CBZ) was

the most frequent, followed by clobazam (CLB) and phenobarbital (PB). The mean follow-up interval after surgery was of 4.7±1.66(one to eight) years.Forty-nine patients (42.6%) were seizure-free (Engel IA) at the moment of the study, whereas 31 patients (26.9%) were Engel IB/IC/ID, 23 (20%) were Engel II, ten (8.7%) were Engel III, and two (1.8%)were Engel IV. Pre-surgical PD occurred in 47 patients (40.8%), while post-surgical PD occurred in 31 (26.9%). Pre-surgical PD observed in both groups of patients are described in Figure 1.

We found no significant differences between the two groups was seen when all the others clinical and socio-demographic variables were analyzed, except for pre-surgical PD, which was associated to a non-favorable seizure outcome (p=0.002) in the initial model. See Table 1.

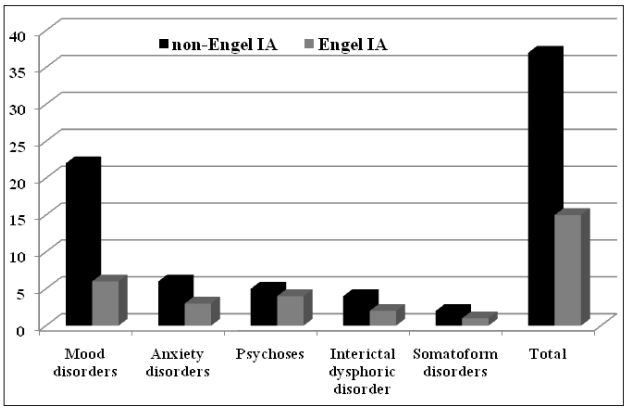

Figure 1. Number and types of pre-surgical psychiatric diagnoses in patients with temporal lobe epilepsy and mesial temporal sclerosis submitted to anterior temporal lobectomy.

Table 1. Clinical and demographic data from temporal lobe epilepsy and mesial temporal sclerosis patients submitted to anterior temporal lobectomy.

Clinical/demographic data	Engel IA	Non-Engel IA	*P*
Number of patients (%)	49 (42.6)	66 (57.4)	-
Age at surgery (mean ± SD)	36.7±10.9	37.0±10.7	0.85
Gender-females (%)	26 (53.1)	40 (60.6)	0.45
Age at epilepsy onset (mean ± SD)	10.5±9.0	8.8±7.3	0.28
Years of epilepsy at surgery (mean ± SD)	24.1±12.9	24.2±12.5	0.67
Lifetime psychiatric treatment (%)	12 (24.5)	19 (28.8)	0.67
Family history of epilepsy (%)	12 (24.5)	24 (36.4)	0.22
Family history of psychiatric disorders (%)	5 (10.2)	13 (19.7)	0.20
Presence of febrile seizures (%)	8 (16.3)	17 (25.8)	0.23
Presence of left-sided MTS (%)	29 (59.2)	46 (69.7)	0.32
Presence of pre-surgical PD (%)	13 (26.5)	37 (56.1)	0.002*
Presence of post-surgical PD (%)	11 (22.4)	20 (30.3)	0.40
Disorganized VEEG background activity (%)	9 (18.4)	14 (21.2)	0.81
Contralateral slow-waves on VEEG (%)	12 (24.5)	18 (27.3)	0.97
Contralateral epileptiform discharges on VEEG (%)	15 (30.6)	19 (28.8)	0.64
Years of follow-up (mean ± SD)	4.5±1.6	4.8±1.6	0.27

MTS: mesial temporal sclerosis; SD: standard deviation; PD: psychiatric disorders; VEEG: video-electroencephalographic monitoring.
* $p < 0.05$.

A multivariate logistic regression model was performed (sensivity 78.8%; specificity 71.2%; positive predictive value 73.2%; negative predictive value 68.1%; area under the curve 0.768) to identify possible clinical and socio-demographic risk factors associated to a non-favorable seizure outcome. The presence of any pre-surgical PD was associated to a worse surgical outcome (OR=3.53; p=0.002) at initial model.However, when psychiatric diagnoses were analyzed separately, onlymajor depressive disorderpersisted as statistically significant (OR=5.11; p=0.004), while other PD together (except depression) were not significant (OR=1.62; p=0.34).The presence of post-surgical PD wasnot associated with a worse seizure outcome (OR=1.50; p=0.35), as well as others clinical and socio-demographic variables. Table 2 shows the final adjusted model's results.

Table 2. Logistic regression results: final adjusted model.

Risk factors	Odds ratio	*p>z*
Family history of PD	2.49	0.14
Presence of febrile seizures	4.25	0.06
Lifetime psychiatric treatment	1.69	0.25
Pre-surgical PD (except depression)	1.62	0.34
Post-surgical PD	1.50	0.35
Pre-surgical depression	5.11	0.004*

PD: psychiatric disorders.
* $p<0.05$.

4 DISCUSSION

In the present paper we studied theimpact of pre-surgical PD on the seizure outcome in a homogeneous series of patients with a specific and prevalent epilepsy syndrome submitted to the same surgical procedure (ATL). Psychiatric evaluations were performed by the same diagnostic criteria based on the modern psychiatric nosography.

Surgery became an important treatment option for patients with refractory TLE-MTS and ATL has appeared as a safe and efficient surgical procedure,[1-5] althoughsome authors have highlighted the relative high risk of the appearance of PD in patients submitted to surgical procedure, while other studies do not support such hypothesis.[16,21-24]

Some recent studies consider pre-surgical PD as predictors of seizure outcome after surgery.[12-15] However, most reports consist of patients with heterogeneous epileptic syndromesand followed-upfor limited periods, precluding conclusionsin more specific populations, such as TLE-MTS.[16] Nevertheless, it has been increasingly recognized that a pre-surgical PD could be a significant predictor of seizure outcome after surgery. Literature data have observed that pre-surgical PD, as well as a lifetime history of depressionpredicts a worse post-surgical seizure outcome among patients with refractory TLE. The most discussed hypothesis in literature is that pre-surgical PD, and particularly depression, would be possible epiphenomena of a more diffuse cerebral disease and with a consequently worse seizure control.[13-15] Such observations could reinforce the bidirectionality of the association between depression and postoperative seizure status that could be explained by underlying common pathophysiological mechanisms in both depression and epilepsy.[13-15,25] Moreover, the majority of series reported an association between the absence of post-surgical PD and a better surgical outcome.[21-25] The present study observed a statistically significant association between the absence of pre-surgical PD and a favorable seizure outcome. In addition, pre-surgical major depressive disorder was associated to a worse seizure outcome at the multivariate logistic regression model. Such findings are in accordance with recent data and also support current hypothesis regarding pre-surgical PD and seizure outcome.[13-15]

Although performed in a relatively small number of patients, our observations are in line with recent literature data and strengthenthe importance of the pre-surgical PDin a specific population of TLE-MTS patients. The findings of the present paper are of great value and reinforce the importance of performing a detailed psychiatric pre-surgical evaluation of epilepsy patients,[4,5,13-16] once it showed anassociation between pre-surgical PD and non-favorable seizure outcome.[13-16]

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REFERENCES

1. Falconer MA, Serafetinides EA. A follow-up study of surgery in temporal lobe epilepsy. J Neurol Neurosurg Psychiat 1963;26: 154-65.
2. Wiebe S, Blume WT, Girvin JP, Eliasziw M. For the effectiveness and efficacy of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal lobe epilepsy. N Engl J Med 2001;345:311-8.
3. Foong J, Flugel D. Psychiatric outcome of surgery for temporal lobe epilepsy and presurgical considerations. Epilepsy Res 2007;75: 84-96.
4. Pintor L, Bailles E, Fernández-Egea E, Sánchez-Gistau V, Torres X, Carreño M, et al. Psychiatric disorders in temporal lobe epilepsy patients over the first year after surgical treatment. Seizure 2007;16:218-25.
5. Guarnieri R, Walz R, Hallak JEC, Coimbra E, Almeida E, Cescato MP, Velasco TR, Alexandre Jr. V, Terra VC, Carlotti CGJ, Assirati JAJ, Sakamoto AC. Do psychiatric comorbidities predict postoperative seizure outcome in temporal lobe epilepsy surgery? Epilepsy Behav 2009; 14:529-34.
6. Tellez-Zenteno JF, Wiebe S. Prevalence of psychiatric disorders in patients with epilepsy: what we think we know and what we know. In: Kanner AM, Schachter S (eds.). Psychiatric controversies in epilepsy. San Diego: Academic Press; 2008. p.1-18.
7. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand 2004;110:207-20.
8. Devinsky O. Psychiatric comorbidity in patients with epilepsy: implications for diagnosis and treatment. Epilepsy Behav 2003;4: 2-10.
9. De Araujo Filho GM, Rosa VP, Lin K, Caboclo LO, et al. Psychiatric comorbidity in epilepsy: a study comparing patients with mesial temporal sclerosis and juvenile myoclonic epilepsy.Epilepsy Behav 2008;13:196-201.
10. De Araujo Filho GM, Mazetto L, Macedo JS, Caboclo LO, Yacubian EMT. Psychiatric comorbidity in patients with two prototypes of focal versus generalized epilepsy syndromes. Seizure 2011;20:383-6.
11. Swinkels WAM, Boas WE, Kuyk J, et al. Interictal depression, personality traits and psychological dissociation in patients with temporal lobe epilepsy (TLE) and extra-TLE. Epilepsia 2006;47: 2092-103.
12. Anhoury S, Brown RJ, Krishnamoorthy ES, Trimble MR. Psychiatric outcome following temporal lobectomy: a predictive study. Epilepsia 2000;41:1608-15.
13. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms and treatment. Biol Psychiatry 2003;54: 388-98.
14. Kanner AM, Byrne R, Smith MC, Balabanov AJ, Frey M. Does a lifetime history of depression predict a worse postsurgical seizure outcome following a temporal lobectomy? Ann Neurol 2006;10:19.
15. Kanner AM. Should a psychiatric evaluation be included in every pre-surgical work-up? In: Kanner AM, Schachter S (eds.). Psychiatric controversies in epilepsy. San Diego: Academic Press 2008:239-54.
16. Macrodimitris S, Sherman EMS, Forde S, Tellez-Zenteno JF, Metcalfe A, Hernandez-Ronquilho L, Wiebe S, Jetté N. Psychiatric outcomes of epilepsy surgery: a systematic review. Epilepsia 2011;52:880-90.
17. Commission on Classification and Terminology of the International League Against Epilepsy, 10. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30: 389-99.
18. Engel Jr. J, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel Jr. J (ed.). Surgical treatment of the epilepsies. New York: Raven Press; 1993.

19. American Psychiatric Association. Diagnostic and statistical manual for mental disorders DSM-IV (Text Revision). 4th ed. Washington; 2004.
20. Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE commission on psychobiology of epilepsy. Epilepsy Behav 2007; 10:349-53.
21. Blumer D, Wakhlu S, Davies K, et al. Psychiatric outcome of temporal lobectomy for epilepsy: incidence and treatment of psychiatric complications. Epilepsia 1998;39:478-86.
22. Altshuler L, Rausch R, DeIrahim S, Kay J, Crandall P. Temporal lobe epilepsy, temporal lobectomy and major depression. J Neuropsychiatry Clin Neurosci 1999;11:436-43.
23. Reuber M, Andersen B, Elger CE, Helmstaedter C. Depression and anxiety before and after temporal lobe epilepsy surgery. Seizure 2004;13:129-35.
24. Devinsky O, Barr WB, Vicrey BG, Berg AT, Bazil CW, Pacia SV, Langfit JT, Walczak TS, Sperling MR, Shinnar S, Spencer SS. Changes in depression and anxiety after resective surgery for epilepsy. Neurology 2005;65:1744-52.
25. Metternich B, Wagner K, Brandt A, Kraemer R, Buschmann F, Zentner J, Schulze-Bonhage A. Preoperative depressive symptoms predict postoperative seizure outcome in temporal and frontal lobe epilepsy. Epilepsy Behav 2009;16:622-8.

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Vai acontecer

LIGA BRASILEIRA DE EPILEPSIA

Convocação para Assembleia Geral

São Paulo, 09 de março de 2012.

Prezados associados,

Convocamos todos os associados da Liga Brasileira de Epilepsia (*com anuidade em dia*), para a **Assembleia Geral** que ocorrerá no Centro de Convenções Ribeirão Preto (sala Rubi) durante o XXXIV Congresso Brasileiro de Epilepsia no **dia 08 de junho de 2012**, às **19 horas**, em primeira chamada ou às **19h30min**, em segunda chamada, com a presença de qualquer quorum, e **encerramento às 20h30min**, com a seguinte pauta:

a) Aprovação da Ata da Assembleia Geral de 05 de junho de 2010 realizada durante o XXXIII Congresso Brasileiro de Epilepsia;
b) Comunicados;
c) Relatório da Diretoria Executiva;
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e) Eleição do Conselho Fiscal;
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Presidente da LBE
Biênio 2010-2012

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