UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA:
CIÊNCIAS MÉDICAS

ASPECTOS EPIDEMIOLÓGICOS, GENÉTICOS E ELETROENCEFALOGRÁFICOS DAS COMORBIDADES PSIQUIÁTRICAS DA EPILEPSIA DO LOBO TEMPORAL

Autor: José Augusto Bragatti

Orientador: Marino Muxfeldt Bianchin

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Tese de Doutorado

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FICHA CATALOGRÁFICA

Dedico este trabalho a
meus mestres, meu pai, José Hermínio Bragatti,
que me ensinou a arte do ofício, e a meu professor,
Frederico Arthur Dahne Kliemann, que me legou
a técnica e a ciência da Epileptologia .

AGRADECIMENTOS:

"Há sempre, após uma breve crise epiléptica, um defeito da consciência objetiva – negativo, por assim dizer – e restos positivos dessa consciência, que algumas vezes exacerbam a consciência subjetiva, gerando "um estado de sonho" – positivo, por assim dizer. Em outras palavras, "a condição positiva" é dupla; é um estado mental anormal; imperfeito por deficiência, e imperfeito por excesso."

in The Selected Writings of John Hughlings Jackson

SUMÁRio

1. RESUMO

A associação entre transtornos psiquiátricos e epilepsia do lobo temporal é frequente, embora ainda não esteja totalmente esclarecida em termos epidemiológicos. Há um crescente entendimento das complexas relações entre as duas condições, em termos genéticos, fisiopatológicos e neurofisiológicos. No entanto, ainda há muito para desvendar nesta área, e existe uma grande oportunidade, nos dias atuais, de serem utilizadas modernas ferramentas diagnósticas, sobretudo nos campos da biologia molecular e da neuroimagem, de serem desvendados vários mistérios que seguem pairando a respeito dessa associação.

Esta tese dedicou-se a estudar a prevalência de comorbidades psiquiátricas na epilepsia do lobo temporal (ELT), a influência genética de dois polimorfismos referentes ao sistema serotoninérgico na expressão clínica destas comorbidades, e também estudou aspectos neurofisiológicos ligados à frequência de descargas interictais no EEG dos pacientes com ELT, buscando correlações com comorbidades psiquiátricas nestes pacientes.

No primeiro capítulo, apresentamos um artigo de revisão sobre aspectos epidemiológicos, características clínicas, e implicações terapêuticas e prognósticas da presença de comorbidades psiquiátricas nos indivíduos com epilepsia. Mecanismos fisiopatológicos, com envolvimento de circuitos neurais comuns à epilepsia e a diversos transtornos psiquiátricos foram propostos.

No segundo capítulo, nós avaliamos a presença de transtornos psiquiátricos numa população de pacientes com epilepsia do lobo temporal do nosso meio, utilizando como método diagnóstico uma entrevista clínica

estruturada, baseada nos critérios diagnósticos do DSM-IV. Foram estudados 98 pacientes (59 mulheres, 39 homens) com média de idade de 43 anos, e tempo de duração média da sua epilepsia de 25 anos. Foi observado pelo menos um diagnóstico psiquiátrico ao longo da vida em 54% dos nossos pacientes. O transtorno psiquiátrico mais frequente foi o transtorno de humor, observado em 43% dos pacientes, seguido por transtornos de ansiedade, presente em 18% da população estudada. Transtornos psicóticos e abuso de álcool ou outras substâncias estiveram presentes em 6% dos indivíduos estudados cada. Presença de descargas epileptiformes no lobo temporal esquerdo aumentou em sete vezes o risco dos pacientes com ELT apresentarem algum transtorno psiquiátrico. A prevalência de transtornos psiquiátricos encontrada foi superior à encontrada na literatura, possivelmente devido a diferenças na amostra estudada, e principalmente por diferentes métodos diagnósticos utilizados nos demais estudos referentes ao tema. No entanto, o nosso estudo ressaltou a importância da padronização do método diagnóstico empregado em futuras pesquisas sobre o assunto.

No terceiro capítulo desta Tese, estudamos a influência dos polimorfismos do gene *TPH2* (*Tryptophan Hydroxylase 2)*, que sintetiza uma enzima limitante das taxas de serotonina na fenda sináptica, sobre a frequência de transtornos psiquiátricos na ELT. Nesse artigo, nós estudamos a influência dos polimorfismos rs4570625 e rs17110747 do gene *TPH2* em 163 pacientes com ELT, nos quais aplicamos o SCID, uma entrevista psiquiátrica estruturada. Neste estudo, a presença do alelo T do polimorfismo rs4570625 aumentou em 6 vezes as chances do paciente com ELT apresentar algum transtorno psiquiátrico, enquanto a presença do alelo A no polimorfismo rs17110747

aumentou em 20 vezes as chances do paciente com ELT ser abusador de álcool. Neste estudo, sexo masculino e história familial psiquiátrica foram fatores de risco independentes para abuso de álcool na ELT. Já história familial de epilepsia esteve inversamente correlacionada com abuso de álcool nos pacientes estudados. O estudo ressaltou a importância do sistema serotoninérgico na expressão de doenças psiquiátricas associadas à ELT.

Finalmente, no quarto capítulo, nós quantificamos as descargas epileptiformes interictais no EEG de 78 pacientes com ELT, a fim de determinar a influência desta atividade sobre a presença de comorbidades psiquiátricas nestes pacientes. Foi observado que pacientes com um diagnóstico de transtorno de humor ao longo da vida apresentaram um índice significativamente mais baixo de descargas interictais (inferior a um evento por minuto), um possível correlato neurofisiológico do fenômeno da Normalização Forçada, um dos componentes das complexas relações existentes entre Depressão e Epilepsia.

2.   ABSTRACT

The association between psychiatric disorders and temporal lobe epilepsy is common, though not yet fully understood in epidemiological terms. There is a growing genetic, pathophysiological and neurophysiological understanding of the complex relationship between the two conditions. However, there is still much to uncover in this area, and there is great opportunity, today, to be used modern diagnostic tools, especially in the fields of molecular biology and neuroimaging, being unraveled many mysteries that follow hovering about this association.

This thesis is devoted to study the prevalence of psychiatric comorbidities in temporal lobe epilepsy (TLE), the influence of two genetic polymorphisms related to the serotonergic system in the clinical expression of these comorbidities, and also to study neurophysiological aspects related to the frequency of interictal discharges in the EEG in TLE patients, seeking correlations with psychiatric comorbidities in these patients.

In the first chapter, we present a review article on epidemiological, clinical, and therapeutic and prognostic implications of the presence of psychiatric comorbidities in individuals with epilepsy. Pathophysiological mechanisms, involving common neural circuits to epilepsy and different psychiatric disorders have been proposed.

In the second chapter, we evaluated the presence of psychiatric disorders in a population of patients with TLE in our midst, using as a diagnostic method a structured clinical interview, based on the diagnostic criteria of the DSM-IV. We studied 98 patients (59 women, 39 men) with a mean age of 43

years and a mean duration of epilepsy of 25 years. At least one lifetime psychiatric diagnosis was observed in 54% of our patients. Mood disorder was the most common psychiatric disorder, observed in 43% of patients, followed by anxiety disorders, present in 18 % of the population. Psychotic disorders and alcohol or other substances abuse were present in 6 % of the subjects each. Presence of epileptiform discharges in the left temporal lobe has increased seven times the risk of patients with TLE presenting any psychiatric disorder. The prevalence of psychiatric disorders was higher than that found in the literature, possibly due to differences in the sample studied, and especially by different diagnostic methods used in other studies on the subject. However, our study highlights the importance of standardizing the diagnostic method used in further research on the subject.

In the third chapter of this thesis, we studied the influence of polymorphisms of *TPH2* (Tryptophan Hydroxylase 2), which synthesizes a rate - limiting enzyme of serotonin in the synaptic cleft, on the frequency of psychiatric disorders in TLE. In this paper, we study the influence of polymorphisms rs4570625 and rs17110747 in *TPH2* gene in 163 patients with TLE, in which we applied the SCID, a structured psychiatric interview. In this study , the presence of the T allele of rs4570625 polymorphism increased by 6 times the chances of the patient with TLE exhibit some psychiatric disorder, while the presence of the A allele at rs17110747 polymorphism increased by 20 times the odds of patients with TLE be an alcohol addict. In this study, male gender and familial psychiatric history were independent risk factors for alcohol abuse in ELT. A family history of epilepsy was inversely correlated with alcohol abuse in the

patients studied. The study highlighted the importance of the serotonergic system in the expression of psychiatric disorders associated with TLE.

Finally, in the fourth chapter, we quantified interictal epileptiform discharges in the EEG of 78 patients with TLE, in order to determine the influence of this activity on the presence of psychiatric comorbidities in these patients. It was observed that patients with a lifelong diagnosis of mood disorder showed a significantly lower interictal discharges (less than one event per minute), a possible neurophysiological correlate of the phenomenon of forced normalization, a component of the complex relationships between depression and epilepsy.

3.   LISTA DE ABREVIATURAS

5-HT: Serotonina

5-HTT: Transportador da Serotonina

5-HTTLPR: do Inglês *Serotonin-transporter-variable number of tandem repeats*

5-HTTVNTR: do Inglês *Serotonin-transporter-linked polymorphic region*

CTN: Células Tronco Neurais

DAE: Drogas Anti Epilépticas

DASB: do Inglês *[11C]-3-Amino-4-(2-Dimethyl Aminomethylphenyl Sulfanyl)-Benzonitrile*

DEI: Descargas Epileptiformes Interictais

DM: Depressão Maior

EEG: Eletroencefalograma

ELT: Epilepsia do Lobo Temporal

EMJ: Epilepsia Mioclônica Juvenil

FCWAY: do Inglês *18F-Trans-4-Fluoro-N-2-[4-(2-Methoxyphenyl) Piperazin-1-yl] Ethyl-N-(2-pyridyl) Cyclohexane Carboxamide*

FDA: do Inglês *Food and Drug Administration*

HMGA2: do Inglês *High-Mobility Group A T-Hook 2*

LTQ: Locus do Traço Quantitativo

MADRS: do Inglês *Montgomery-Åsberg Depression Rating Scale*

PDS: do Inglês *Paroxysmal Depolarization Shift*

PET: do Inglês *Positron Emission Tomography*

RM: Ressonância Magnética

RMf: Ressonância Magnética funcional

SNC: Sistema Nervoso Central

SNP: do Inglês *Single Nucleotide Polymorphism*

SNRI: do Inglês *Serotonine-Norepinephrine Reuptake Inhibitors*

SSRI: do Inglês *Selective Serotonin Reuptake Inhibitors*

TB: Transtorno Bipolar

TDI: Transtorno Disfórico Interictal

TIRDA: do Inglês *Temporal Intermittent Rhythmic Delta Activity*

TPH: do Inglês *Tryptophan Hydroxylase*

TPH2: do Inglês *Tryptophan Hydroxylase 2*

4.   INTRODUÇÃO

A epilepsia é uma doença neurológica freqüente, presente em indivíduos em todas as partes do mundo, embora a maioria das pessoas com epilepsia (PCE) vivam em países subdesenvolvidos. O termo epilepsia compreende múltiplas condições neurológicas caracterizadas por uma tendência à recorrência espontânea de crises epilépticas. A epilepsia ocorre em todas as idades e pode ser associada a vários problemas cognitivos, sociais e psiquiátricos. [1]

As crises epilépticas são manifestações clínicas (sintomas) que iniciam abruptamente e têm uma grande variabilidade na forma de apresentação. Uma crise pode-se apresentar com alterações motoras, sensoriais, autonômicas e/ou do estado de consciência. [2] O substrato fisiopatológico comum para todos os tipos de crises epilépticas é o desequilíbrio entre influências excitatórias e inibitórias sobre os circuitos neuronais. Em resumo, há um estado de hiperexcitabilidade sustentado pelo predomínio das forças excitatórias sobre as forças inibitórias. As epilepsias e as crises epilépticas são divididas em generalizadas (quando a descarga neuronal anormal apresenta um rápido engajamento a partir de algum ponto de um circuito representado em ambos os hemisférios) e focais (hiperexcitabilidade neuronal envolvendo circuitos limitados a um hemisfério). [3]

A desordem epiléptica mais comum é a epilepsia do lobo temporal (ELT), que aflige 40% dos adultos com epilepsia. [4] As crises do lobo temporal podem pertencer a três tipos distintos: focais com fenômenos sensitivos ou psíquicos (auras), discognitiva com automatismos, e evoluindo para crise convulsiva bilateral. As ELT são divididas em mesiais (origem no hipocampo e

na amígdala) e laterais (origem no neocórtex temporal). A ELT mesial apresenta alto índice de associação com transtornos psiquiátricos, uma vez que envolve circuitos do Sistema Límbico, o principal integrador de processos emocionais. [5,6] A patologia mais comum causando ELT mesial é a esclerose hipocampal. [2]

Uma crise epiléptica subdivide temporalmente o estado clínico de um PCE em dois períodos de tempo distintos: ictal (ou peri-ictal) e interictal (período em que não ocorre qualquer atividade rítmica neuronal excessiva sustentada). O alvo principal do tratamento farmacológico da epilepsia é a prevenção do fenômeno ictal. Em geral, isto é alcançado em cerca dois terços dos casos.[1] No entanto, o estudo do período interictal dos PCE também é muito importante, e tem aumentado a compreensão da fenômeno epiléptico como um todo.

Uma das questões mais importantes não ligada ao controle farmacológico das crises é a avaliação das comorbidades no PCE. Estes pacientes têm um risco aumentado para distúrbios cognitivos, comportamentais e psicossociais. [6,7] Neste sentido, não apenas um pobre controle das crises epilépticas, mas também a presença de comorbidades pode afetar diretamente qualidade de vida do PCE. Existe um risco aumentado de suicídio em PCE, compardo à população em geral, e esse risco é ainda maior em pacientes com uma história de transtorno psiquiátrico, especialmente naqueles com uma associação entre depressão e ansiedade. [8]

A associação entre epilepsia e transtornos mentais é uma condição já conhecida desde a Antiguidade. A maior parte do estigma que acompanha os

PCE é proveniente da atribuição do distúrbio epiléptico a entidades sobrenaturais, como deuses, bruxas e demônios. [9]

A prevalência da associação entre epilepsia e transtornos psiquiátricos varia entre 20 e 50%, podendo chegar a 80% em populações selecionadas, como pacientes com epilepsia do lobo temporal e pacientes refratários, candidatos a tratamento cirúrgico. Estes índices são superiores àqueles encontrados na população geral (10 a 20%). Diferenças metodológicas e entre populações estudadas são os principais fatores responsáveis pela variabilidade de resultados encontrados. Também diferentes definições epidemiológicas (prevalência pontual, prevalência cumulativa, prevalência ao longo da vida) têm significados próprios, contribuindo igualmente para a variabilidade de resultados. [10, 11]

Os fatores de risco para as principais comorbidades psiquiátricas em pacientes portadores de epilepsia (depressão, ansiedade e psicose) têm sido amplamente estudados, e podem ser divididos em fatores (1) neurobiológicos; (2) psicossociais e (3) farmacológicos. Dentre os fatores neurobiológicos, são apontados o tipo, a duração, a frequência, a idade de início e a lateralização da crise epiléptica, predisposição genética, sexo, presença de lesões estruturais. Também aspectos relativos ao tratamento cirúrgico da epilepsia, como lateralização, tipo de ressecção, diagnóstico histopatológico e prognóstico cirúrgico têm sido estudados. Podem ser destacadas ainda, a perda de volume hipocampal, o hipometabolismo da glicose nos lobos temporal e frontal, alterações de neurotransmissores e substâncias neuroendócrinas. Como fatores psicossociais, podemos citar o assim chamado "desespero aprendido", restrições às atividades normais da vida diária, com resultantes baixa auto

estima, dificuldades educacionais e profissionais, estigmatização e rejeição social. Dentre os fatores farmacológicos, têm sido citados os efeitos colaterais de DAEs depressoras do sistema nervoso central (SNC), a suspensão de DAEs estabilizadoras do humor, politerapia, início de uma nova DAE, ou ajuste de doses em meio ao tratamento. [12, 13]

As evidências não favorecem uma associação homogênea entre subgrupos de epilepsias e transtornos psiquiátricos. Na maioria dos pacientes, uma grande variedade de fatores de risco crônicos e agudos pode ser identificada. Estes fatores são difíceis de investigar retrospectivamente, o que nem sempre permite estabelecer uma relação de causa e efeito. A literatura dos fatores de risco é altamente controversa, e há uma enorme dificuldade para comparar os diferentes estudos, devido à variabilidade na definição de termos fundamentais como "epilepsia", "transtorno psiquiátrico", e os próprios fatores de risco investigados.

É importante salientar que não existe uma relação causa-efeito unidirecional entre epilepsia e transtornos mentais, ou seja, não só a condição epiléptica pode preceder a instalação dos sintomas psiquiátricos num determinado paciente, mas também o diagnóstico de transtornos afetivos e comportamentais podem ocorrer previamente a uma primeira crise epiléptica de um paciente. Esta bidirecionalidade sugere que alterações estruturais e funcionais de uma doença aumentam o risco para o desenvolvimento da outra. [14]

São crescentes as evidências que, na epilepsia e nos transtornos psiquiátricos, uma alteração da interação entre neurônios serotoninérgicos e noradrenérgicos com sistemas glutamatérgicos está associada a circuitos

neuronais anormais e hiperexcitabilidade. Esta hiperexcitabilidade pode evocar tanto atividade de crise quanto alterações emocionais. [13]

Há evidências crescentes que o sistema serotonérgico tem participação fundamental tanto nos mecanismos básicos da associação entre epilepsia e uma série de transtornos psiquiátricos, quanto no grau de severidade, e, portanto, sobre o prognóstico do transtorno epiléptico. [15-18]

Neste trabalho procuramos avaliar o impacto dos polimorfismos ligados aos genes receptores e transportadores da serotonina sobre o prognóstico clínico dos pacientes com epilepsia, avaliando particularmente associações entre estes polimorfismos e comorbidades psiquiátricas, e também sobre o grau de epileptogênese do transtorno epiléptico, expressado pelo índice de descargas epileptiformes interictais encontrado no EEG destes pacientes. Inicialmente, realizamos um estudo de prevalência das comorbidades psiquiátricas em pacientes com epilepsia do lobo temporal.

Os resultados do trabalho foram apresentados em 4 artigos, dois deles já publicados, e os outros dois ainda em fase de revisão. O primeiro artigo é uma revisão sobre aspectos epidemiológicos, características clínicas, e implicações terapêuticas e prognósticas da presença de comorbidades psiquiátricas nos indivíduos com epilepsia.

No segundo artigo, nós avaliamos a presença de transtornos psiquiátricos numa população de pacientes com epilepsia do lobo temporal do nosso meio, utilizando como método diagnóstico uma entrevista clínica estrurada, baseada nos critérios diagnósticos do DSM-IV. Foram estudados 98 pacientes (59 mulheres, 39 homens) com média de idade de 43 anos, e tempo de duração média da sua epilepsia de 25 anos. Foi observado pelo menos um

diagnóstico psiquiátrico ao longo da vida em 54% dos nossos pacientes. O transtorno psiquiátrico mais frequente foi o transtorno de humor, observado em 43% dos pacientes, seguido por transtornos de ansiedade, presente em 18% da população estudada. Transtornos psicóticos e abuso de álcool ou outras substâncias estiveram presentes em 6% dos indivíduos estudados cada. Presença de descargas epileptiformes no lobo temporal esquerdo aumentou em sete vezes o risco dos pacientes com ELT apresentarem algum transtorno psiquiátrico. A prevalência de transtornos psiquiátricos encontrada foi superior à encontrada na literatura, possivelmente devido a diferenças na amostra estudada, e principalmente por diferentes métodos diagnósticos utilizados nos demais estudos referentes ao tema. No entanto, o nosso estudo ressaltou a importância da padronização do método diagnóstico empregado em futuras pesquisas sobre o assunto.

No terceiro artigo desta Tese, estudamos a influência dos polimorfismos do gene *TPH2* (*Tryptophan Hydroxylase 2)*, que sintetiza uma enzima limitante das taxas de serotonina na fenda sináptica, sobre a frequência de transtornos psiquiátricos na ELT. Nesse artigo, nós estudamos a influência dos polimorfismos rs4570625 e rs17110747 do gene *TPH2* em 163 pacientes com ELT, nos quais aplicamos o SCID, uma entrevista psiquiátrica estruturada. Neste estudo, a presença do alelo T do polimorfismo rs4570625 aumentou em 6 vezes as chances do paciente com ELT apresentar algum transtorno psiquiátrico, enquanto a presença do alelo A no polimorfismo rs17110747 aumentou em 20 vezes as chances do paciente com ELT ser abusador de álcool. Neste estudo, sexo masculino e história familial psiquiátrica forma fatores de risco independentes para abuso de álcool na ELT. Já história familial

de epilepsia esteve inversamente correlacionada com abuso de álcool nos pacientes estudados. O estudo ressaltou a importância do sistema serotoninérgico na expressão de doenças psiquiátricas associadas à ELT.

Finalmente, no quarto artigo, nós quantificamos as descargas epileptiformes interictais no EEG de 78 pacientes com ELT, a fim de determinar a influência desta atividade sobre a presença de comorbidades psiquiátricas nestes pacientes. Foi observado que pacientes com um diagnóstico de transtorno de humor ao longo da vida apresentaram um índice significativamente mais baixo de descargas interictais (inferior a um evento por minuto), um possível correlato neurofisiológico do fenômeno da Normalização Forçada, um dos componentes das complexas relacioções existentes entre Depressão e Epilepsia.

5.   REVISÃO DA LITERATURA

Pesquisamos a base de dados Pubmed (Pubmed.gov), utilizando as seguintes palavras chave: *epilepsy, psychiatric comorbidities, alcohol and substance abuse, EEG, interictal epileptiform discharges, serotonin, e TPH2*.

Foram localizados 39297 artigos, dos quais 248 foram incluídos na Revisão Sistemática para esse estudo. Foi dada preferência para artigos publicados nos últimos 10 anos, e para artigos de revisão. Também foram pesquisados livros texto consagrados sobre o tema da Tese, e incluídas referências de capítulos destes livros.

5.1. Comorbidades Psiquiátricas em Epilepsia

5.1.1. Histórico

A associação entre epilepsia e transtornos psiquiátricos tem sido descrita desde o início da prática da Neurologia e da Psiquiatria, e são vários os exemplos encontrados na literatura. Hipócrates, já por volta do ano 400 AC, observou uma dicotomia entre epilepsia e melancolia, propondo que estas entidades estariam ligadas por um provável mecanismo fisiopatológico comum. [9]

A história da interface entre epilepsia e psiquiatria teve seu inicio marcado pela associação empírica destas condições com deuses, bruxas, demônios e fenômenos sobrenaturais. Os gregos referiam-se à epilepsia como a "doença sagrada". Nesta época, Hipócrates supôs que o ataque de fúria que motivou Hércules a matar seus filhos tinha uma origem epiléptica. Os romanos referiam-se à epilepsia como "morbidus lunaticus", relacionando-a com as

diferentes fases da lua. No mundo árabe, a associação entre epilepsia, doença mental e demônios persistiu, e profetas como Maomé e São Paulo, que, dizia-se, periodicamente ouviam vozes e caíam ao solo, supostamente sofriam de epilepsia. [19]

No século XIX e no início do século XX, epilepsia era um diagnóstico comum em asilos de pacientes com doença mental. Os mais graves eram tratados por psiquiatras, enquanto os menos graves permaneciam na comunidade, onde eram tratados por clínicos gerais ou por neurologistas. [20]

As observações de Emil Kraepelin, na década de 1920, são consideradas a base da classificação diagnóstica psiquiátrica moderna. Kraepelin descreveu precisamente as alterações afetivas dos pacientes com epilepsia antes da era da terapia anticonvulsivante. Episódios disfóricos, caracterizados por irritabilidade, com ou sem ataques de fúria, segundo ele, representavam o transtorno psiquiátrico mais comum da epilepsia. Depressão, ansiedade, cefaléia e insônia frequentemente completavam o quadro clínico, enquanto humor eufórico era menos comum. [21]

Heinrich Landolt identificou diferentes tipos de episódios psicóticos e suas relações com crises epilépticas e o eletroencefalograma (EEG), introduzindo o conceito de "psicose alternante ou normalização forçada". [22] Seu trabalho foi complementado posteriormente por Slater e Beard, com o artigo "Psicose do Tipo Esquizofrenia da Epilepsia", que propunha uma relação agônica entre as crises epilépticas e os estados psicóticos. [23]

Mais recentemente, a introdução de técnicas avançadas de neuroimagem, como a tomografia por emissão de positrons (PET), a ressonância magnética do encéfalo (RMN) e a espectroscopia, combinadas a

modelos animais e testes comportamentais refinados, tornou possível a identificação de mecanismos fisiopatológicos comuns às epilepsias (sobretudo a do lobo temporal) e transtornos psiquiátricos (sobretudo a depressão maior).

5.1.2. Epidemiologia

Há poucos estudos sobre prevalência de condições psiquiátricas em epilépticos na população geral. A maioria dos estudos envolve populações específicas de epilépticos, em centros de atenção terciária em epilepsia. Estudos epidemiológicos baseados na população geral sugerem uma prevalência de transtornos psiquiátricos ao longo da vida em pacientes epilépticos, tanto adultos quanto crianças, entre 20 e 50%. [11, 24-32] Recentemente, Tellez-Zenteno e colaboradores, utilizando dados do Registro de Saúde Comunitária Canadense e aplicando o CIDI (*Composite International Diagnostic Interview*), encontraram uma prevalência de 35% de transtornos psiquiátricos ao longo da vida em pacientes epilépticos, contra 20% em indivíduos não epilépticos. [7]

A grande variabilidade de resultados obtidos tem sido atribuída a diferenças de metodologia empregada e de populações estudadas. É sabido que psicopatologias psiquiátricas podem estar superestimadas em populações selecionadas, como nos pacientes com ELT ou naqueles com crises refratárias [33], onde a prevalência de transtornos mentais pode chegar a 80%. [34]

5.1.3. Métodos de avaliação psiquiátrica

Os métodos de avaliação psiquiátrica dividem-se em entrevistas estruturadas e questionários autoaplicáveis. [10] As entrevistas não estruturadas

vêm sendo progressivamente abandonadas nos últimos anos em favor de entrevistas estruturadas, que possuem maior precisão diagnóstica. As entrevistas estruturadas constituem-se numa lista de perguntas chaves que visam preencher critérios bem definidos de diagnósticos contemplados no Manual Diagnóstico e Estatístico das Doenças Mentais (DSM-IV). Os principais representantes são a Entrevista Clínica Estruturada para o DSM-IV (*SCID*) [35] e a Mini Entrevista Neuropsiquiátrica Internacional (*MINI*). [36] Questionários autoaplicados, como o Inventário de Depressão de Beck (*BDI*) [37], e a Escala de Depressão do Centro para Estudos Epidemiológicos (*CES-D*) [38], em geral são menos extensos e baseiam-se em critérios subjetivos. Os resultados obtidos com testes autoaplicados tendem a superestimar as prevalências dos transtornos psiquiátricos.

De qualquer forma, os estudos de prevalência de transtornos psiquiátricos ao longo da vida em pacientes epilépticos apontam para índices superiores àqueles encontrados na população geral (10 a 20%). [39]

5.1.4. Fatores de risco

Vários artigos demonstraram que pacientes com ELT têm um risco aumentado para a presença de transtornos psiquiátricos, quando comparados a pacientes com epilepsia focal extratemporal, epilepsia generalizada idiopática, e outras doenças crônicas. [5, 34, 40-42] No entanto, ainda é controverso se pacientes com ELT apresentam risco aumentado de desenvolver transtornos mentais, quando comparados a pacientes com outros tipos de epilepsia. Dois importantes estudos não encontraram diferenças de risco entre pacientes com ELT, epilepsias focais extratemporais e

generalizadas idiopáticas. [43, 44] É possível que a prevalência aumentada de transtornos psiquiátricos em pacientes com ELT represente simplesmente a frequência aumentada da ELT em relação às outras epilepsias. [45]

É plausível, no entanto, supor que os mesmos circuitos neuronais envolvidos na fisiopatogênese da epilepsia do lobo temporal sejam também responsáveis pela produção de sintomas psiquiátricos. [13] Os mecanismos propostos para esta frequente associação dividem-se, arbitrariamente, em causas clínicas, biológicas e ambientais. Têm sido apontados como fatores clínicos: (1) o número de crises epilépticas ocorridas desde o início da doença (diretamente relacionado à idade de início e ao tempo de duração da epilepsia); (2) o efeito das medicações utilizadas no tratamento da epilepsia; (3) a lateralidade do foco irritativo (hemisfério dominante x não dominante); (4) o sexo e (5) a história familial psiquiátrica. [6]

Fatores biológicos dizem respeito a alterações químicas e estruturais envolvendo os circuitos do Sistema Límbico, sede do processamento do comportamento e das emoções. [12] Os fatores ambientais possivelmente envolvidos na produção de comorbidades psiquiátricas em epilepsia incluem a perda da independência, o estigma social, as limitações legais (ex.: licença para dirigir veículos) e financeiras. [46] Num estudo prospectivo realizado na Universidade de Nova Iorque, Devinsky e colaboradores avaliaram o impacto de diversas variáveis clínicas sobre a qualidade de vida em pacientes com epilepsia refratária, internados para a realização de vídeo-EEG. Presença de depressão, avaliada através do BDI, foi o único fator preditivo para índices baixos obtidos no Questionário sobre Qualidade de Vida em Epilepsia (QOLIE-31). Frequência de crises, localização da crise, idade, sexo, situação marital,

duração e tipo de crise, e número de drogas antiepilépticas (DAEs) utilizadas não foram preditores de qualidade de vida, nesse estudo. [47]

Pacientes com epilepsia têm um risco de suicídio significativamente maior do que a população geral. Dois grandes estudos, realizados no Canadá [7] e na Dinamarca [8], demonstraram que o risco de suicídio é 2 a 3 vezes maior em pacientes epilépticos quando comparados com indivíduos controles. O estudo dinamarquês encontrou um risco de suicídio ainda maior entre epilépticos portadores de uma comorbidade específica: transtorno de humor com ansiedade.

5.1.5. Transtornos psiquiátricos específicos

a) Transtornos de Humor

Especificamente para depressão em epilepsia, têm sido estudados fatores de risco neurobiológicos: (1) lateralidade do foco de crise; (2) hipometabolismo frontal; e (3) volume do hipocampo.

Com relação à lateralidade do foco, Hurwitz et al.[48] encontraram associação entre crises epilépticas iniciadas no hemisfério esquerdo e humor depressivo; neste estudo, crises originadas no hemisfério direito acompanharam-se de risos e comportamento sedutor. Como a atividade de crise num hemisfério possivelmente "libere" o hemisfério contralateral, os autores postularam que o hemisfério dominante seria responsável por estados emocionais negativos, e o hemisfério não dominante produziria um efeito oposto. Outra teoria postula que uma atividade de crise no hemisfério não dominante poderia resultar em negligência das emoções negativas [45] Alguns

estudos controlados comparando foco de crise com graus de depressão encontraram frequências aumentadas de depressão com foco no hemisfério esquerdo, independente do tipo de crise [49-52], enquanto outros estudos não confirmaram esta associação.[53] Uma complexa interação entre vários fatores deve estar implicada nesta associação.

Recentes trabalhos utilizando PET e SPECT têm demonstrado uma associação entre epilepsia e disfunção com hipometabolismo do lobo frontal. Bromfield e colaboradores estudaram 23 pacientes com crises parciais complexas, candidatos a cirurgia, quanto a manifestações depressivas (BDI>11), comparando-os a controles normais. Os pacientes com foco temporal à esquerda tiveram mais manifestações depressivas, e apresentaram um hipometabolismo frontal inferior bilateral. [54] Victoroff et al.[52], também estudando uma população de 53 epilépticos candidatos a tratamento cirúrgico, encontraram que um início ictal à esquerda associou-se a uma frequência maior de depressão (79% x 50%, não significativa). Não foi encontrada nenhuma correlação entre o estado afetivo corrente e o metabolismo nos lobos frontais, porém, foi interessante observar que uma história de depressão (identificada pelo SCID) correlacionou-se significativamente a um hipometabolismo do lobo frontal esquerdo. Hermann et al. não encontraram correlação entre humor e lateralidade, porém um foco localizado à esquerda esteve significativamente associado ao grau de disfunção frontal (avaliada pelo *Wisconsin Card Sort Test*) e disforia. [55] Ao contrário, um foco à direita foi inversamente associado ao grau de disfunção frontal e disforia (resultados não significativos).

Poucos estudos avaliaram a associação entre perda de volume hipocampal, depressão e epilepsia. Quiske e colaboradores encontraram maiores escores de BDI em pacientes com ELT e esclerose temporal mesial, quando comparados a pacientes com RMN normal. [56] Outro estudo identificou uma associação de escores maiores para depressão com maiores volumes de hipocampo esquerdo em pacientes com esclerose hipocampal direita. [57] Também estudos com PET demonstraram uma associação entre maiores escores de depressão em epilépticos com alterações metabólicas nos lobos temporais em relação a epilépticos com PET normal. [58]

Um tema imprtante, ao tratarmos de transtornos de humor em pacientes com epilepsia, é a questão sobre até que ponto o transtorno epiléptico modifica a expressão clínica da Depressão e outros transtornos afetivos. Psiquiatras pré-moderna, como Kraepelin e Bleuler, observaram que os pacientes com epilepsia podiam desenvolver um transtorno de humor caracterizado por um padrão pleomórfico de sintomas, como depressão misturada com euforia, irritabilidade, medo e ansiedade, bem como anergia, dor e insônia. [59, 60] Este conceito foi revitalizado durante o Século XX por Blumer, que cunhou o termo Transtorno Disfórico Interictal (TDI) para se referir a esse tipo de transtorno somatoforme-depressivo, hipotetizado como típico de pacientes com epilepsia. [61] Esta condição é um transtorno de humor, provavelmente não específico para a epilepsia, que é normalmente diagnosticada durante a fase depressiva, com uma ansiedade associada (fobia social e/ou transtorno de ansiedade generalizada), e um componente relevante da instabilidade de humor. [62] No entanto, uma série de características atípicas e pleomórficas desta condição estão relacionadas com sintomas peri-ictais [63] que, na verdade, são típicos

apenas de pacientes com epilepsia. Esta questão tem relevantes implicações em termos de prognóstico e tratamento. Por um lado, enfatiza a necessidade de dissecar as manifestações peri-ictais das interictais, sendo as primeiras relacionadas ao prognóstico e tratamento da síndrome epiléptica. Por outro lado, a presença de instabilidade de humor como um elemento essencial do TDI sugere a necessidade de prescrever DAE estabilizadoras do humor como o tratamento de escolha, e o uso de drogas antipsicóticas em casos selecionados.

b) Transtornos de Ansiedade

Os principais tipos de transtorno de ansiedade descritos no DSM-IV são: (1) transtorno de ansiedade generalizada (TAG); (2) transtorno do pânico; (3) fobia; e (4) transtorno obsessivo compulsivo. Os fatores de risco estudados para ansiedade e epilepsia são: (1) frequência de crises; (2) tratamento cirúrgico para a epilepsia; (3) idade; (4) tipo de crise; e (5) percepção do estigma. [64, 65]

A frequência de crises foi associada à ansiedade em alguns trabalhos [66, 67], mas não em todos. [68] Estudos com PET associados a dados eletrofisiológicos apontam para o lobo temporal direito como a principal estrutura responsável na patogênese da ansiedade em epilepsia. [69] Parece que, mais do que a frequência das crises, o medo de cair ou morrer é que se constitui num fator crítico para o desenvolvimento da ansiedade nos epilépticos. O tratamento cirúrgico para a epilepsia pode aumentar a frequência de transtornos epilépticos. Num estudo, pacientes com mais de 75% de redução de crises experimentaram mais sintomas de ansiedade. [70]

Quanto à idade do paciente, efeitos mínimos foram observados, podendo um início tardio de epilepsia estar associado a maiores níveis de ansiedade. [71] O risco de ansiedade parece ser maior nas epilepsias focais (especialmente ELT) do que nas generalizadas. [72] Índices mais altos de ansiedade foram encontrados em pacientes refratários ao tratamento clínico. [73, 74] Um importante fator ligado à ansiedade em epilépticos é a percepção do estigma [75, 76], e este fator é maior em pacientes mais jovens.[69, 77]

A co-ocorrência de transtornos depressivos e de ansiedade também é relativamente freqüente em pacientes com epilepsia. Por exemplo, em um estudo de base populacional, a taxa de prevalência de transtornos de ansiedade encontrada foi 22,8% dos pacientes com epilepsia, contra 11% em indivíduos sem epilepsia, enquanto uma taxa de 34% foi encontrada para a coexistência de ansiedade e transtornos depressivos. [7]

Transtornos de ansiedade são também relativamente freqüentes em pacientes com epilepsia tratados em centros especializados de epilepsia. Em um estudo de 188 pacientes consecutivos com epilepsia, de cinco centros de epilepsia dos EUA (50% dos quais livres de crises nos últimos seis meses), 83 apresentavam uma comorbidade de transtorno psiquiátrico. Distúrbios de ansiedade no momento do estudo foram identificados em 49 pacientes (26%). Dentre esses 49 pacientes, 28 eram portadores de coexistência entre ansiedade e transtornos depressivos; destes, 27 pacientes (14,4%) tinham dois ou mais transtornos de ansiedade. [78]

c) Transtornos psicóticos

Os transtornos psicóticos encontrados em pacientes com epilepsia são divididos de acordo com a relação temporal de manifestação dos sintomas psicóticos com as manifestações de crise do paciente. Assim, as psicoses em pacientes epilépticos podem ser ictais, pós-ictais ou interictais. A literatura a respeito de fatores de risco para psicose em epilepsia é altamente controversa, e a maioria dos estudos se restringem às psicoses interictais. [79]

Com relação à duração da epilepsia, o intervalo entre o início da epilepsia e a primeira manifestação de psicose, na maioria das séries, encontra-se em torno de 11 a 15 anos, suscitando um significado etiológico para o transtorno epiléptico, através de um mecanismo tipo *kindling*. [80] A ELT é a epilepsia com maior associação com psicose, em quase todas as séries de casos. Numa revisão não sistemática de 10 estudos, 76% dos pacientes com psicose tinham também ELT. [20] No entanto, a maior crítica feita a estes estudos é que os seus resultados podem estar simplesmente refletindo a maior prevalência de ELT na população geral. Um dos fatores de risco mais fortes para psicose em epilepsia é a severidade da epilepsia, representada pela duração, múltiplos tipos de crise, história de estado epiléptico e pouca resposta clínica ao tratamento. [20] Flor-Henry [80] sugeriu originalmente que disfunção do lobo temporal esquerdo é fator de risco para psicose esquizofreniforme. A análise de 14 estudos de Trimble com 341 pacientes com ELT encontrou que 43% tinham foco à esquerda, 23% à direita, e 34% alterações bilaterais. [20] Estes achados de lateralidade foram apoiados por estudos de neuroimagem, especialmente SPECT e RMN. Mellers et al. [81], utilizando um paradigma de ativação de fluência verbal e SPECT, comparou pacientes com psicose do tipo esquizofrenia da epilepsia (n = 12), com esquizofrenia (n = 11), e epilépticos

não psicóticos (n = 16). Os epilépticos psicóticos apresentaram um maior fluxo sanguíneo no giro temporal superior, durante a ativação, em relação aos demais grupos. Já Maier et al.[82], compararam os volumes amígdalo-hipocampais e o N-acetil aspartato (NAA) hipocampal (por espectroscopia) de pacientes com ELT, com (n = 12) e sem psicose do tipo esquizofrenia (n = 12), esquizofrênicos sem epilepsia (n = 26), e indivíduos normais (n = 38). Os pacientes psicóticos apresentaram significativa redução do NAA no LT esquerdo, e este fenômeno foi mais acentuado em pacientes epilépticos. Os epilépticos apresentaram reduções de volume bilaterais, enquanto os psicóticos tiveram uma atrofia mais acentuada no complexo amigdalo-hipocampal esquerdo.

A psicose interictal parece ser diferente da esquizofrenia, principalmente por cursar com mais sintomas afetivos e por ter um melhor prognóstico. Enquanto alterações hipocampais podem estar relacionadas a ambos os transtornos, o aumento bilateral das amígdalas (com menores alterações volumétricas dos hipocampos) é característico da psicose interictal, sugerindo que ambos são biologicamente muito distintos. Esta hipótese é apoiada num estudo recente, com 26 pacientes com psicose epiléptica, 24 com ELT e sem psicose, e 20 controles normais. Os pacientes psicóticos tiveram aumentos significativos, bilaterais, das amígdalas, comparados aos outros grupos. Os achados não se correlacionaram com a lateralidade do foco, nem com o tempo de duração da epilepsia do paciente. [83]

d) Abuso de álcool e outras substâncias

A síndrome da dependência do álcool é definida como um conjunto de fenômenos fisiológicos, comportamentais e cognitivos nos quais a utilização de álcool assume uma prioridade muito mais elevada para um dado indivíduo que outros comportamentos que antes tinham maior valor. Ela está associada com uma vasta gama de doenças orgânicas, mentais e sociais, e a custos econômicos e sociais enormes. A prevalência da dependência de álcool entre a população adulta varia entre 2 e 12% nas populações da Europa Ocidental e da América do Norte. [84] Num estudo transversal, a prevalência de abuso de álcool na zona urbana do município de Rio Grande (RS), em indivíduos de 12 a 75 anos de idade, foi de 5,5%. A dependência de álcool na população estudada foi de 2,5%. [85]

Os critérios de diagnóstico variam entre sintomas físicos e psicológicos. Como exemplo, os critérios de diagnóstico do DSM-IV são: tolerância, sintomas de abstinência ou o uso de álcoois para evitar ou aliviar sintomas de abstinência, beber mais do que o pretendido, tentativas sem sucesso de reduzir o uso, tempo excessivo dispendido ao álcool (obtenção, ressaca), atividades sociais ou de trabalho prejudicadas pelo uso de álcool, e uso continuado apesar de consequências físicas ou psicológicas. [86]

Abuso/dependência de álcool é mediada por mecanismos neurais complexos que envolvem o múltiplos circuitos do cérebro, e alterações neuroadaptativas, em uma variedade de sistemas de neurotransmissores e neuropeptíodeos. Embora estudos recentes têm fornecido informações substanciais sobre os mecanismos neurobiológicos que impulsionam o comportamento de beber álcool, persistem desafios significativos na

compreensão de como neuroadaptações induzidas pelo álcool ocorrem e como diferentes circuitos neurais interagem entre si. [87]

Os estudos genéticos sobre o alcoolismo têm examinado o metabolismo do álcool, e os sistemas neurotransmissores dopaminérgicos, GABAérgicos, glutamatérgicos, opióides, colinérgicos e serotonérgicos, bem como o neuropeptídeo Y. [88] O papel do gene do transportador de serotonina no diagnóstico de alcoolismo continua a ser controverso. O número de estudos sobre os genes de receptores da serotonina também é muito limitado, e com resultados controversos. [89]

Uma recente meta-análise revlou uma forte e consistente associação entre consumo de álcool e epilepsia (risco relativo: 2,19) [90] O consumo crônico de álcool tem diversos efeitos sobre o sistema nervoso central, afetando sua estrutura e funcionamento de várias maneiras: o álcool promove o desenvolvimento de atrofia cerebral, além do que outras alterações estruturais, tais como infartos cerebrovasculares, lesões e traumatismos cranianos, foram mais prevalentes em usuários pesados de álcool e pessoas com dependência ao álcool, tendo sido diretamente relacionados a crises epilépticas repetidas em vários estudos. [91, 92]

O álcool tem diversos efeitos agudos e crônicos sobre o metabolismo e a função cerebrais, que já foram amplamente estudados. [93] No entanto, estudos genéticos de associação entre alcoolismo e outras doenças neurológicas, em especial epilepsia, são escassos na literatura. [89]

5.1.6. Relação bidirecional

Está demonstrado que alguns transtornos afetivos e comportamentais específicos podem apresentar uma relação bidirecional com o início de crises epilépticas, ou seja, um diagnóstico psiquiátrico pode anteceder o início de crises em três situações: depressão maior, ideação suicida e transtorno do déficit de atenção com hiperatividade (TDAH).

Tanto em estudos de caso-controle [94, 95], quanto em estudos longitudinais em crianças [96], foi encontrado um risco aumentado de 2,5 vezes em pacientes com diagnóstico de TDAH sofrerem uma primeira crise epiléptica.

Três estudos controlados avaliaram a relação temporal entre depressão e epilepsia. Um estudo de caso-controle, baseado na população geral, encontrou um risco sete vezes aumentado de um adulto com depressão desenvolver epilepsia, em relação aos indivíduos controles. Nas epilepsias focais, este risco aumentou para 17 vezes. [27] Hesdorffer et al.[97] encontraram a mesma relação temporal entre depressão e primeira crise, com um risco 6 vezes maior. Os dados destes dois estudos foram confirmados num estudo controlado, baseado na população geral, realizado na Islândia, com 324 pacientes acima de 10 de anos de idade, com uma primeira crise não provocada ou epilepsia recém-diagnosticada, e 647 controles: depressão maior, diagnosticada segundo os critérios do DSM-IV, aumentou o risco para epilepsia em 1,7 vezes. Este mesmo estudo demonstrou que uma tentativa de suicídio está associada com um risco aumentado em 3,5 vezes para epilepsia. [14]

5.1.7. Mecanismos fisiopatogênicos comuns

Esta relação de bidirecionalidade sugere uma susceptibilidade subjacente comum à epilepsia e a transtornos afetivos. Dados ligando as duas doenças envolvem níveis molecular, celular e regional no cérebro. [98] Estes mecanismos são fortemente interligados, e as alterações funcionais e estruturais de uma doença podem desencadear a outra.

a) Modelos animais

Um dos mais bem estudados modelos de ELT usa substâncias convulsivantes, como cainato e pilocarpina, injetadas, em geral, de forma sistêmica. Após provocar um estado de mal epiléptico no animal, segue-se, no modelo, um período de latência de algumas semanas, após o qual se desenvolvem crises espontâneas. [99] Outro modelo experimental utilizado é o *kindling* elétrico. No entanto, este método não parece reproduzir os eventos fisiopatológicos da ELT tão fidedignamente quanto o método farmacológico, pois as crises não ocorrem espontaneamente, não se desenvolve uma esclerose hipocampal, e não há um período de latência entre o insulto precipitante inicial e o desenvolvimento das crises.

Recentemente, Mazarati et al.[100] investigaram se um aumento crônico da suscetibilidade a crises induzida por *kindling* resultava num comportamento depressivo em ratos. Duas a quatro semanas após a aplicação de 84 estímulos elétricos (a cada cinco minutos) subconvulsivantes no hipocampo ventral de ratos Wistar adultos, os investigadores aplicaram dois testes: o teste do nado forçado (TNF), e o teste da gustação (preferência por açúcar). Uma imobilidade no tanque, no TNF, é equivalente à depressão, pois o animal não demonstra

nenhuma iniciativa de fuga de uma situação de estresse. O segundo teste tenta reproduzir a perda da habilidade da busca pelo prazer, frequente na depressão. O estudo demonstrou que os ratos submetidos ao *kindling* exibiam um aumento significativo do tempo de imobilidade no TNF, associado a perda da preferência por gosto adocicado, quando comparados aos controles. Os autores concluíram que as alterações de plasticidade neuronal causadas pelo *kindling* são acompanhadas por um comportamento depressivo.

O papel dos neurotransmissores no mecanismo fisiopatogênico dos transtornos afetivos é reconhecido desde há algumas décadas. [101] Os papéis do ácido gama-aminobutírico (GABA) e do glutamato na epileptogênese já foram demonstrados em inúmeros estudos com animais e em humanos. O Rato Geneticamente Predisposto à Epilepsia (GEPR) proporciona um modelo experimental tanto para epilepsia quanto para depressão. Neste modelo, os animais portadores da mutação são altamente sensíveis a estímulos auditivos, aos quais eles respondem com crises tônico-clônicas generalizadas (TCG). Além disto, os GEPRs apresentam alterações endocrinológicas semelhantes àquelas identificadas em pacientes com depressão maior: níveis séricos elevados de corticosteróides, secreção diminuída do hormônio do crescimento, e hipotireoidismo. [102] Arborizações deficientes dos circuitos noradrenérgicos e serotoninérgicos foram demonstrados nestes animais. Um aumento dos níveis destes neurotransmissores pode prevenir a ocorrência de crises, enquanto reduções têm o efeito oposto. [102] Um estudo clássico demonstrou que a fluoxetina, um inibidor seletivo da recaptação sináptica da serotonina, provocou uma redução dose-dependente da frequência de crises em GEPRs, que se correlacionou com a concentração serotoninérgica talâmica extracelular. [103]

b) Estudos em humanos

Transmissão serotoninérgica anormal foi demonstrada no cérebro de pacientes deprimidos [104, 105], mesmo achado encontrado nos estudos com PET, em pacientes com ELT. [106, 107] Num estudo mais recente, Hasler et al. compararam o nível de ligação dos receptores 5-HT1A a um antagonista específico, em 37 pacientes com ELT, com e sem depressão maior (diagnóstico por SCID), utilizando PET. Além de uma diminuição da ligação aos receptores 5-HT1A no foco epiléptico, os pacientes com depressão maior exibiam uma redução da ligação mais extensa, envolvendo áreas não límbicas, distantes do foco epiléptico. [108]

5.2. O Sistema Serotoninérgico e Epilepsia

O neurotransmissor Serotonina (5-Hidroxitriptofano – 5-HT) está envolvido em diversas doenças neurológicas e psiquiátricas, e várias medicações neuropsiquiátricas atuam sobre seus receptores. A 5-HT presente no cérebro é produzida por um número relativamente pequeno de neurônios localizados nos núcleos medianos da rafe do mesencéfalo, ponte e bulbo.[109] Existe uma alta densidade de fibras e terminais serotonérgicos distribuídos por todo o SNC, incluindo o hipocampo e o neocórtex.

Estudos utilizando PET demonstraram diminuição da ligação aos receptores 5-HT no córtex frontal, temporal e límbico de pacientes com transtornos depressivos primários, sem epilepsia [110], no lobo frontal mesial e estruturas do tronco encefálico, na ELT [111-115], e no córtex dorsolateral

prefrontal, núcleos da rafe e hipocampo, na EMJ. [116] Na ELT, ligações reduzidas aos receptores 5-HT$_{1A}$ são encontradas em estruturas temporais mesiais, ipsilaterais ao foco epileptogênico (hipocampo, amígdala, giro do cíngulo), e no hipocampo contralateral ao foco.

Pacientes com ELT e transtorno depressivo maior apresentam ligação diminuída aos receptores 5-HT$_{1A}$ no foco epiléptico, estendendo-se até áreas límbicas não lesionais fora do foco epileptogênico. Pacientes com ELT sem depressão têm redução destas ligações mais restritas ao foco. [114] Uma correlação inversa entre gravidade dos sintomas de depressão e ligação aos receptores 5-HT$_{1A}$ no hipocampo ipsilateral ao foco epiléptico também foi observada na ELT.[115] Achados semelhantes foram encontrados utilizando espectroscopia por ressonância magnética.[117]

Na EMJ, ligação diminuída aos receptores 5-HT$_{1A}$ foi observada no córterx prefrontal dorsolateral, núcleos da rafe e hipocampos, quando comparados aos controles. [116] Esta síndrome epiléptica apresenta níveis elevados de comorbidade com depressão e ansiedade. [118]

Várias DAE, incluindo Fenitoína, Carbamazepina, Ácido Valproico, Lamotrigina e Zonisamida, causam um aumento de 5-HT extracelular, o que se acredita contribuir para os mecanismos de ação destes fármacos. [15, 119-122]

O efeito anticonvulsivante dos SSRI, observado em modelos animais de epilepsia, foi também sugerido por diversos estudos abertos de pacientes com epilepsia farmacorresistente. Por exemplo, Citalopram diminuiu 55,6% a frequência média de crises em pacientes com epilepsia mal controlada e sem depressão. [123] Além disto, o antidepressivo Imipramina, com efeitos inibitórios

sobre a recaptação da noradrenalina e 5-HT, suprimiu crises de ausência e mioclônico astáticas, em estudos duplo-cego controlados por placebo. [124,125]

Portanto, o 5-HT pode ter propriedades anticonvulsivantes, um efeito possivelmente mediado pelos autorreceptores 5-HT$_{1A}$ dos núcleos da rafe. Esta impressão é apoiada por um recente estudo de coorte, examinando crises epilépticas como eventos adversos em estudos clínicos randomizados da FDA, com SSRI e SNRI para tratamento de Depressão Maior. [126] Neste estudo, observou-se um risco 19 vezes aumentado para crises epilépticas no grupo placebo com Depressão Maior, comparado com a frequência esperada na população geral. Além disto, comparado com o grupo placebo, o grupo tratado com antidepressivos foi significativamente protegido para o desenvolvimento de crises.

Não há evidências para mutações em genes diretamente envolvidos com a via serotoninérgica em síndromes epilépticas humanas, mas uma deleção genética dos receptores 5-HT$_{2C}$ em camundongos causam crises audiogênicas [127], e deleção dos receptores 5-HT$_{1A}$ reduz o limiar para crises induzidas por cainato. [128] Num estudo seminal, investigando 8 diferentes polimorfismos relacionados com genes codificadores de receptores de 5-HT, e também relacionados com o transportador da 5-HT, não encontrou nenhuma associação entre essas variantes genéticas e a ELT. [129] No entanto, estudos subsequentes encontraram um papel de determinados polimorfismos de genes da serotonina com comorbidades psiquiátricas (ansiedade) [130] e distúrbio de memória [131] em pacientes com ELT.

Além de anormalidades nos receptores 5-HT, estudos em pacientes com transtornos de humor sugerem um papel para o transportador da serotonina (5-

HTT), que modula a recaptação da 5-HT na fenda sináptica. [132-136] Indivíduos com 1 ou 2 cópias do alelo curto do promotor do 5-HTT, têm mais sintomas depressivos, depressão diagnosticada, e tendência ao suicídio, relacionados a eventos estressantes, do que homozigotos para o alelo longo.[137] Um estudo recente utilizando PET com DASB (uma molécula que se liga ao 5-HTT) e FCWAY (ligante com receptores $5-HT_{1A}$), avaliou pacientes com ELT, com e sem depressão. Os autores concluíram que há uma redução da atividade transportadora na ínsula e no giro fusiforme de pacientes com ELT e depressão, comparado a indivíduos com ELT apenas, implicando uma recaptação reduzida, e, portanto aumento da disponibilidade sináptica de 5-HT nestas regiões. Este achado pode representar um mecanismo compensatório à perda de receptores $5-HT_{1A}$. [138]

5.3. O Gene Transportador da Serotonina

O 5-HTT é o principal regulador do nível de neurotransmissão serotonérgica, sendo o principal fator de inativação da 5-HT. [139] Após a liberação pelos neurônios pré-sinápticos, a ação da 5-HT como um modulador químico é encerrada primariamente pela sua recaptação via 5-HTT. O gene humano *5-HTT* está localizado no cromossomo 17q11.1-q12, abrange 31 kb, e consiste de 14 exons.[140] Dois polimorfismos do gene *5-HTT* demonstraram consequências funcionais: 5-HTTLPR e 5-HTTVNTR. O polimorfismo 5-HTTLPR é uma inserção/deleção com 44 pares de base na região 5' do gene *5-HTT*. Ele origina 2 alelos: S ("*short*") e L ("*long*"). O alelo S foi associado a uma menor eficiência transcricional do gene *5-HTT*, resultando numa menor

captação de 5-HT, quando comparado com o alelo L.[141] O polimorfismo 5-HTTVNTR é um número variável de repetições em sequência, contendo 9, 10 e 12 repetições de uma sequência de 17 pares de base localizados no intron 2. O domínio 5-HTTVNTR atua como regulador da transcrição, e o alelo 12 está associado a uma maior atividade transcricional do gene *5-HTT*, quando comparado com o alelo 10.[142]

Schenkel et al.[143] encontraram uma associação entre a combinação bialélica do polimorfismo 5-HTTLPR e uma menor eficiência transcricional do polimorfismo 5-HTTVNTR, com pacientes com ELT comparados a indivíduos controle. Os autores hipotetizaram que uma função transcricional reduzida nos polimorfismos estudados estariam associados a níveis elevados de 5-HTT durante o desenvolvimento cerebral, causando alterações funcionais e inibindo a expansão do sistema serotonérgico, e aumentando assim, o risco para o desenvolvimento de transtornos neuropsiquiátricos e de epilepsia límbica em idades mais avançadas.[144-147]

Um estudo caso-controle [148] encontrou associação entre uma menor frequência de 10 repetições e uma menor frequência de indivíduos homozigotos para o alelo 10 do polimorfismo 5-HTTVNTR com ELT. Resultado oposto (maior frequência da frequência do alelo de 10 repetições) foi encontrado num estudo realizado numa população chinesa. [149] Outra associação relacionada a um polimorfismo localizado no intron 2 do gene 5-HTT com refratariedade ao tratamento da ELT foi encontrada em outro estudo exploratório.[150] Indivíduos homozigotos para o alelo de 12 repetições apresentaram um risco aumentado de quase 4 vezes para ausência de

resposta ao tratamento clínico, comparados a homozigotos para o alelo de 10 repetições.

O conjunto destes trabalhos indica um papel do gene *5-HTT* e suas variantes genéticas na suscetibilidade individual para o desenvolvimento de ELT em humanos.

5.4. A Proteína TPH2

Triptofano hidroxilase (TPH) é a enzima limitadora da taxa de biossíntese da serotonina. Ela converte o aminoácido triptofano em 5-hidroxitriptofano, que é então descarboxilado em serotonina. [151] Duas isoformas, *TPH1* e *TPH2*, são conhecidas. Enquanto o *TPH1* é majoritariamente expressa na periferia e apenas parcialmente no cérebro, o *TPH2* é exclusivamente expressa em alguns neurônios [152], particularmente nos dos núcleos da rafe, onde a grande maioria dos neurônios serotoninérgicos estão localizados.[151, 153, 154] Após a descoberta de que camundongos "*TPH2-knockout*" e *TPH1*-homozigotos TPH1 continuaram a produzir 5-HT no cérebro, mas não em outros tecidos[151], tem sido dada cada vez mais atenção ao papel do homólogo humano do TPH2, localizado no cromossomo 12q21, em doenças mentais, uma vez que esta é uma região candidata posicional para vários transtornos psiquiátricos, tais como depressão maior (DM) e transtorno bipolar (TB).[155-159]

Além disso, tendo em conta o papel significativo da serotonina no controle do humor, e de uma ampla variedade de funções, incluindo regulação do sono, percepção da dor, atividade hormonal, cognição, e níveis de agressão

sexual, apetite e energia[160], não é surpresa que grandes esforços têm sido dispendidos para se descobrir que papéis as variantes genéticas do *TPH2* poderiam desempenhar no desenvolvimento e na resposta ao tratamento de vários transtornos psiquiátricos. Na verdade, a serotonina é amplamente envolvida tanto nos transtornos do humor, como na esquizofrenia, como demonstrado pelo efeito terapêutico dos moduladores de serotonina nestes distúrbios mentais.

Os resultados sugerem um possível envolvimento do *TPH2* na etiologia e resposta às drogas na DM. Em primeiro lugar, nos pacientes com depressão sem tratamento farmacológico que cometeram suicídio, foram encontrados níveis de proteína TPH e de *mRNA TPH2* no núcleo dorsal da rafe significativamente maiores, quando comparados com controles saudáveis pareados.[161,162] Além disso, estes pacientes tinham maior densidade de TPH2 no núcleo dorsal da rafe do que os controles.[162] Num modelo animal que expressa uma variante do gene *TPH2* semelhante a uma variante humana rara (R441H) previamente associada a DM, a expressão de tais mutantes *TPH2* resultou numa redução acentuada da produção cerebral de 5-HT, e levou a anormalidades comportamentais relacionados à depressão e ansiedade.[163]

Vários estudos de caso-controle têm sugerido que diversas variantes genéticas do gene *TPH2* podem estar associados a DM, tanto em pacientes caucasianos[164-168], quanto chineses[169] que sofrem de DM, embora resultados contrastantes têm sido relatados.[170-173] Além disso, diversas variantes do gene *TPH2* têm sido associadas com níveis de resposta a antidepressivos[165, 169,174, 175], bem como à terapia electroconvulsiva[176] em muitas amostras

independentes, incluindo diferentes etnias, embora os resultados nem sempre tenham sido replicados.[173, 177]

Também tem sido sugerido que variantes do gene *TPH2* possam desempenhar um papel no TB. Níveis mais elevados de expressão TPH2 foram encontrados no córtex prefrontal dorsolateral de pacientes com TB, em comparação com controles pareados.[178] Além disso, vários estudos de caso-controle encontraram associações significativas entre polimorfismos de nucleotídeo único (SNPs) específicos e haplótipos dentro do gene *TPH2* e TB, em amostras incluindo principalmente indivíduos caucasianos[167, 179-183], embora tais resultados não tenham sido consistentemente replicados em outras amostras de caucasianos[184, 185], bem como em sujeitos coreanos com TB.[186] Vale a pena mencionar, contudo, que , embora um conjunto de SNPs localizados na região 5 ' do gene *TPH2*, anteriormente associado com TB em uma amostra alemã, não tenha sido replicado numa população romena[185] , tal associação foi significativa em um subgrupo de pacientes com transmissão paterna da doença, levantando a questão de algumas variantes *TPH2* serem específicas para alguns subpopulações de pacientes, mas não para outras. Além disso, recentes resultados[181] sugerindo a existência de interações epistáticas entre TPH2 e TPH1 ressaltam a importância de considerar que interações genéticas complexas poderiam regular o risco de uma determinada doença, em comparação com os genes individuais analisados separadamente.

Na sequência dessas conclusões, uma série de estudos começou a se concentrar em um possível papel do TPH2 na esquizofrenia. No entanto, embora limitada a poucas investigações, a pesquisa experimental sobre esta tema não encontrou provas para um possível envolvimento de diversas

variantes do gene *TPH2* na etiologia da esquizofrenia [187-190], a não ser por uma alteração na expressão do *TPH2* no córtex prefrontal dorsolateral de pacientes com esquizofrenia ,quando comparados a pacientes sofrendo de TB e controles saudáveis.[178] Por outro lado , um certo número de estudos centrado principalmente no polimorfismo rs4570625 , um SNP localizado na região promotora putativa do gene *TPH2* [191], encontraram uma associação com vários transtornos psiquiátricos, incluindo transtorno de pânico [192], transtorno obsessivo- compulsivo [193], e déficit de atenção com hiperatividade. [194] No entanto, tendo em conta a ausência de repetições , tais resultados devem ser considerados com cautela e merecem mais investigações .

Em geral, esses resultados sugerem que diversas variantes genéticas do*TPH2* podem desempenhar um papel importante na etiologia de vários transtornos psiquiátricos, bem como na resposta a alguns de seus tratamentos, muito embora não exista ainda um consenso completo no que diz respeito ao variantes específicas envolvidas. Não há estudos com relação ao envolvimento de polimorfismos do gene *TPH2* nas epilepsias, nem tampouco nas comorbidades psiquiátricas a elas associadas. No entanto, é plausível imaginar que exista um papel destes polimorfismos nas desordens epilépticas, bem como nas comorbidades psiquiátricas a elas associadas.

Serretti e colaboradores, estudando as variantes rs4570625, rs10748185, rs11179027, rs1386498, rs4469933, and rs17110747 do gene *TPH2*, não encontraram nenhuma associação entre essas e qualquer transtorno psiquiátrico. No entanto, em pacientes com DM, haplótipos heterozigotos das variantes rs4570625 e rs10748185 tiveram escores mais elevados de gravidade da doença, medidos pelo MADRS, embora não

apresentassem diferenças quanto à resposta ao tratamento medicamentoso.
[158] No entanto, uma metanálise de 27 estudos encontrou uma forte associação
entre a variante rs4570625 do gene TPH2 e Transtorno Depressivo Maior. [159]

5.5. Polimorfismos do Gene *TPH2* e abuso de álcool

A influência dos polimorfismos do gene *TPH2* sobre a dependência de
álcool tem tido resultados controversos na literatura. Vários estudos não
encontaram diferenças na distribuição das frequências dos haplótipos deste
gene em indivíduos dependentes de álcool, comparados a controles normais.
[195-198] No entanto, um estudo experimental recente demonstrou que uma
deficiência dos níveis de serotonina no cérebro determina o aumento no
consumo de álcool, e também dimimui a sensibilidade de camundongos aos
efeitos sedativos do etanol. [199]

Um único estudo demonstrou uma fraca associação entre polimorfismos
do gene TPH2 e abuso de álcool e comportamento suicida. [200] Além disso, os
autores observaram um comportamento mais impulsivo, e tendência à
agressão verbal no subgrupo dos portadores de polimorfismos do gene TPH2 e
dependentes de álcool.

5.6.   EEG E EPILEPSIA

O Eletroencefalograma (EEG) é o exame complementar mais útil para o
diagnóstico de epilepsia. Mesmo com o advento de métodos mais sofisticados
de neuroimagem para detectar danos estruturais, epilepsia é hoje um dos

poucos problemas clínicos comuns que exigem avaliação EEG de rotina.[201] O EEG é capaz de responder a três questões fundamentais na avaliação diagnóstica dos pacientes com suspeita de epilepsia[202]: (1) o paciente tem epilepsia?; (2) onde está localizada a zona epileptogênica?; (3) quão eficaz está sendo o tratamento?

A descarga epileptiforme (ponta, onda aguda) interictal permanece sendo a marca da epilepsia, e demonstra claramente a hiperexcitabilidade cortical e hipersincronia, além de estar presente no estado interictal "normal". A presença de uma descarga interictal ajuda a confirmar o diagnóstico clínico de epilepsia, auxilia na definição da síndrome epiléptica, fornece informações que auxiliam no planejamento da administração de medicamentos, e ajuda a avaliar candidatura à cirurgia de epilepsia.[203]

O EEG interictal é um registro relativamente barato e fácil de obter, a partir de eletrodos coclocados no couro cabeludo, durante 20-40 min. Se necessário, pode se registrado por um tempo mais longo (muitas horas ou vários dias), quer no próprio laboratório ou com um dispositivo de gravação portátil. No entanto, o registro EEG de rotina está sujeito a certas limitações, que podem impedir a detecção de descargas intercríticas.[204-206] O período de tempo relativamente curto de gravação de um EEG de rotina pode ser insuficiente para detectar descargas interictais que eventualmente ocorram com pouca freqüência.

Eletrodos de escalpo tiram amostras de apenas um terço do córtex, de modo que as descargas originadas dentro de sulcos, nas regiões basais (ex.: córtex orbitofrontal), ou de regiões inter hemisféricas (ex.: córtex motor inter hemisférico suplementar) podem não ser detectadas. Atividades epileptiformes

geradas por um córtex oculto, como a amígdala e o hipocampo, podem não ser capturadas em registros do escalpo.[204] Osso, dura máter e tecido do couro cabeludo podem atenuar mais ainda o sinal do EEG, prejudicando a sensibilidade de um registro de couro cabeludo.[19]

A orientação do dipolo de uma descarga deve ser idealmente ortogonal à superfície, e dipolos que são paralelos ao couro cabeludo podem não ser detectados por eletrodos colocados no couro cabeludo. Uma grande área de córtex, aproximadamente 6 cm^2, precisa estar envolvida para que uma descarga possa ser por eletrodos de escalpo.[207]

Registros do couro cabeludo são sujeitos a artefatos, que podem se sobrepor ao EEG. Descargas interictais podem ser falsamente localizadas ou podem ser discordantes de uma monitorização ictal extra ou intracraniana.[208, 209] Embora confiabilidade entre os eletroencefalografistas adequadamente treinados seja elevada, no mundo real, erros na interpretação do EEG não são incomuns.

5.6.1. Sensibilidade e Especificidade

Raramente, o eletroencefalograma de um indivíduo normal pode mostrar descargas epileptiformes interictais (DEI). Nenhuma descarga epiléptica foi observada num estudo com 100 voluntários saudáveis.[210] Um estudo com mais de 13.000 jovens do sexo masculino candidatos a tripulação aeronáutica mostrou DEI em 0,5% (em 58% deles somente durante a fotoestimulação). [211] Quarenta e três desses indivíduos foram seguidos até os 29 anos, e apenas um indivíduo desenvolveu epilepsia. Os autores concluíram que a chance de

indivíduos saudáveis com DEI no EEG desenvolverem epilepsia é de 2-3%.[211] Num estudo com video EEG com duração média de 6,9 dias de longo prazo de vídeo, foram detectadas DEI em 81% dos pacientes.[212]

DEI são mais comuns em crianças normais, entre 1 e 15 anos de idade (prevalência em torno de 1-2%).[213] A maioria das DEI em crianças são chamadas descargas epileptiformes focais benignas da infância e podem ocorrer nas regiões centrotemporal, frontal e occipital.[214] As crianças mais jovens mais freqüentemente exibem descargas occipitais. Apenas cerca de 8% dessas crianças desenvolvem epilepsia.[215] Cerca de 2% dos pacientes com distúrbios neurológicos, mas não epilepsia têm DEI.[216] Dependendo da idade e epileptogenicidade, descargas epilépticas ocorrem em até 98% dos pacientes com epilepsia.[217]

Inicialmente, o EEG de um paciente com epilepsia pode ser normal em 12-50% das vezes. [218, 219] A repetição do EEG, no entanto, aumenta a acurácia diagnóstica.[220] Registros prolongados também aumentam a chance de captura de DEI. Procedimentos de ativação, como a hiperventilação, a fotostimulação, e a privação de sono aumentam a sensibilidade diagnóstica da EEG.

Um EEG incluindo vigília e sono, e após privação parcial de sono, mostrou DEI em cerca de 50% dos pacientes com um diagnóstico clinicamente provável de epilepsia, nos quais um EEG de rotina, incluindo o estágio II de sono, não revelou DEI. [221] No entanto, o valor do EEG de rotina após uma primeira crise não provocada é controverso. Alguns autores não iniciam tratamento após uma primeira crise. [222] Outros enfatizam que o risco de recorrência de crises é aumentado se o EEG mostra DEI. [223] A decisão de

tratamento anticonvulsivante depende claramente da etiologia da epilepsia e do risco de recorrência de crises individual.

Não há uma definição objetiva para DEI. [224] Mesmo eletroencefalografistas experientes às vezes discordam sobre o diagnóstico de DEI, e, portanto, a interpretação do EEG é prejudicada pela baixa confiabilidade. [225] Transientes agudos normais (variantes epileptiformes benignas) têm de ser diferenciados de "verdadeiras" descargas epilépticas, para evitar uma interpretação errônea (pontas em paliçada, descargas de pequenas pontas, pontas positivas 14-6 Hz). Alguns padrões de EEG que não são epilépticos podem ser supervalorizados, levando a um diagnóstico de epilepsia. [202] A polaridade do transiente agudo é importante para a interpretação, pois o componente mais proeminente das descargas epilépticas é tipicamente negativo. [224] Descargas positivas são raras e podem ser encontradas em pacientes que foram submetidas a procedimento neurocirúrgico. [226]

5.6.2. Descargas Epileptiformes Interictais

Atividade epileptiforme interictal é um termo eletrográfico que descreve o aparecimento abrupto de pontas ou ondas agudas, muitas vezes acompanhadas por ondas lentas. Ao contrário da atividade epileptiforme ictal, são limitadas no tempo e não evoluem em freqüência e/ou distribuição ao longo do tempo. Embora o termo "interictal" pareça implicar a ausência de um distúrbio comportamental concomitante, a definição de atividade epileptiformes interictal não inclui a função neuropsicológica. [227]

Epilepsias focais são caracterizadas pelo desarranjo funcional de uma população restrita de neurônios corticais, que, por várias razões, sofrem de uma condição de aumento da excitabilidade. Os diversos padrões de atividade epileptiforme comumente observados nas epilepsias focais representam a expressão das alterações dinâmicas na excitação e sincronização que ocorrem dentro do agregado de neurônios "epilépticos". A caracterização e a localização no cérebro dos achados EEG observados entre as crises nas epilepsias humanas são cruciais para identificar diferentes síndromes epilépticas, e, portanto, devidamente determinar o tratamento e prognóstico do distúrbio epiléptico. [228]

O termo DEI inclui potenciais de rápida duração, chamadas pontas (eventos síncronos com menos de 50 ms) e potenciais mais lentos (50-200 ms de duração) chamado ondas agudas (Kooi, 1966; Chatrian et al, 1974;. Gotman, 1980; Walczac e Jayakar, 1997). [229-232] Tem sido demonstrado que uma DEI isolada está associada a uma descarga abrupta caracterizada por uma breve seqüência de potenciais de ação rápidos (200-500 Hz), sobreposto a um potencial de despolarização lenta (chamado *PDS – paroxysmal depolarization shift*), conforme demonstrado em diversos modelos experimentais de epilepsia.[229]

Estudos com RM funcional (RMf) demonstraram que uma DEI pode ser um evento danoso que afeta uma grande parte do cérebro, e impede seu funcionamento normal por centenas de milissegundos, pelo menos, e isto tem sido documentado por testes comportamentais. [233]

A localização exata das descargas epilépticas é crucial para a localização da zona epileptogênica, particularmente em pacientes candidatos a

cirurgia da epilepsia. [234] Desde os primórdios do uso do EEG, é reconhecido que DEI temporais anteriores são freqüentemente associadas com epilepsia do lobo temporal (ELT). [235] O advento da ressonância magnética (RM) permitiu identificar esclerose mesial temporal como a etiologia da epilepsia, e a considerar tratamento cirúrgico em muitos destes pacientes, já que grande parte deles não é controlada apenas com tratamento médico. [236] Pacientes com ELT apresentam com freqüência DEI independentes em ambos os lobos temporais. A ocorrência de DEI temporais estritamente unilaterais tem um excelente valor preditivo para a cirurgia de epilepsia bem sucedida na ELT. [237] A predominância de DEI nas regiões temporais mesial (eletrodos F7/F8) e lateral (T3-T5/T4-T6) aponta para uma ELT mesial ou lateral, como foi evidenciado por lesão na RM ou com o uso de EEG invasivo. [238] Pacientes com ELT mesial, como resultado de esclerose hipocampal, e que mostram DEI freqüentes, apresentam um pior prognóstico para cirurgia da epilepsia (28,6% livres de crises) do que pacientes com DEI raras (80,5% livres de crises). [239] No entanto, DEI temporais mesiais não indicam necessariamente ELT. EEG em pacientes com epilepsias extratemporais também têm uma tendência a exibir DEI temporais. [240] Apesar desta tendência, tipicamente as DEI estão localizadas predominantemente no lobo epileptogênico. No entanto, alguns pacientes com epilepsias extratemporais não apresentam nenhuma DEI nos seus EEGs. [241]

Alentecimento regional da atividade EEG não é específico e, portanto, não suporta o diagnóstico de epilepsia. No entanto, a presença de uma atividade lenta rítmica pode auxiliar na localização da zona epileptogénica, uma vez que o diagnóstico de epilepsia esteja estabelecido. Atividade lenta interictal

rítmica nas regiões temporais (atividade delta rítmica temporal intermitente, *TIRDA*) ocorre em pacientes com epilepsias focais. [242]

Portanto, DEI interictais não são apenas uma ferramenta clínica para orientar o tratamento da epilepsia. Eles são também uma janela para a anatomia, gravidade e implicações funcionais da epilepsia.

5.6.3. Índice de Descargas Epileptiformes Interictais

DEI são um biomarcador para a fisiopatologia subjacente da condição epiléptica. [243] DEI frequentes (>60/h) são um forte preditor de um resultado cirúrgico desfavorável, enquanto DEI menos freqüentes prevêm um melhor resultado. [239] Embora a predominância unilateral de DEI seja muitas vezes considerada útil na lateralização da zona de início de crise, no grupo de pacientes com atrofia hipocampal unilateral, a predominância unilateral de DEI (>90%) não é um preditor significativo do resultado cirúrgico.

Rosati e colaboradores demonstraram que os pacientes com ELT com raras DEI têm uma forma menos grave de epilepsia do que aqueles com uma maior taxa anormalidades epileptiformes no EEG interictal. [244] Uma explicação plausível para estes resultados é o fato de que DEI temporais vistas no EEG de escalpo são geradas no neocórtex temporal, e DEI confinadas ao hipocampo não podem ser vistas em tais registros, mesmo com o auxílio de eletrodos temporais inferiores ou esfenoidais. [245] Portanto, uma alta freqüência de DEI temporais no EEG de superfície indica não apenas que o córtex temporal lateral também está envolvido na geração da descarga eléctrica interictal, mas que também ele tem potencial epileptogênico. No mínimo, DEI freqüentes

podem indicar que existe uma região epileptogênica mais extensa, e, portanto um processo epiléptico mais intenso. [243]

Por outro lado, uma baixa taxa de DEI não necessariamente indica um potencial epileptogênico. Achados de atrofia hipocampal unilateral na RM parecem representar uma indicação confiável de que a epilepsia do paciente é unilateral, mesmo que algumas DEI contralaterais estejam presentes. [243]

A frequência de DEI também é um fator prognóstico fundamental no paciente com ELT, conforme Janszky e colaboradores demonstraram. [246] Estudando 303 pacientes com ELT refratária, e portanto, candidatos à cirurgia, utilizando detector automático de pontas, os autores observaram que uma alta frequência de DEI estava associada à maior duração da epilepsia do paciente, e a uma frequência de crises clínicas mais elevada. É importante salientar que a taxa de DEI é significativamente aumentada durante o registro de sono, e esta influência é dependente da idade de início e da duração da epilepsia do paciente. [247, 248]

6.   JUSTIFICATIVA

a) Epilepsia é uma doença comum, principalmente em países em desenvolvimento. A patologia é causa direta de enormes prejuízos pessoais, sociais e financeiros. Portanto, pesquisas que possam melhorar o tratamento dessas patologias podem ter impacto no cuidado da saúde dessas populações.

b) O conhecimento dos fatores genéticos e neurofisiológicos em epilepsia humana é incipiente, mas altamente relevante. Esta é, portanto uma das áreas mais promissoras em pesquisa de epilepsia. Ela que pode fornecer as bases para conhecermos melhor essa patologia, identificar indivíduos susceptíveis precocemente, contribuindo assim, para o delineamento de novos tipos de tratamento para esses pacientes.

c) Estudos que visam identificar pacientes com mau prognóstico clínico são cruciais. A identificação precoce de pacientes que podem evoluir mal clinicamente, pode motivar modificações de estratégias terapêuticas precoces nesses pacientes.

d) Esse tipo de estudo pode fornecer importantes detalhes sobre os mecanismos da epilepsia e das alterações neuropsiquiátricas a elas associadas.

e) Pesquisas que objetivem o estudo da prevalência de comorbidades psiquiátricas em epilepsia são fundamentais para determinar o vulto de

condições médicas associadas à epilepsia, que possam alterar desfavoravelmente seu prognóstico.

f) Estudos como o proposto aqui, podem potencialmente contribuir de forma significativa para o desenvolvimento de novos fármacos pra o tratamento das epilepsias.

g) O projeto proposto é altamente relevante e pode ser realizado com custo relativamente baixo.

h) Os resultados desse estudo podem potencialmente beneficiar uma parte considerável da população, principalmente a população mais carente, cuja prevalência de epilepsia chega a ser 3 vezes superior àquela das classes socialmente mais favorecidas.

7.   OBJETIVOS

A. Objetivos Principais

1.   Estudar a prevalência e a distribuição de transtornos psiquiátricos na Epilepsia do Lobo Temporal na nossa população.

2.   Estudar a influência dos polimorfismos dos genes ligados ao Sistema Serotoninérgico na associação Epilepsia do Lobo Temporal – Transtornos Psiquiátricos.

3.   Avaliar a influência da presença de comorbidades psiquiátricas em pacientes com ELT na atividade eletroencefalográfica interictal, sobretudo no índice de descargas epileptiformes encontrados nestes pacientes.

B. Objetivos Secundários

Avaliar o impacto da variabilidade de cada alelo em diferentes aspectos clínicos e eletroencefalográficos da ELT.

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9.   ARTIGOS

9.1. ARTIGO nº 1

PSYCHIATRIC COMORBIDITIES OF EPILEPSY: A REVIEW

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ABSTRACT

People with epilepsy (PWE) have an increased risk for cognitive, behavioral, and psychosocial disorders. The presence of comorbidities may directly affect quality of life of PWE. For example, there is an increased risk for suicide in PWE, compared to the general population. Association between epilepsy and mental disorders is a condition known since Antiquity, and its ranges from 20 to 50%, reaching 80% in selected populations, like individuals with temporal lobe epilepsy (TLE), and medically intractable patients, candidates to surgical treatment, and these indices are far superior to those found in general population (10-20%). Risk factors for the main psychiatric comorbidities in PWE (depression, anxiety and psychosis) are classified in (1) neurobiological, (2) psychosocial, and (3) pharmacological factors. There is a bidirectional relationship between epilepsy and mental disorders, namely, not only the epileptic disorder can antedate settlement of psychiatric symptoms in a given patient, but also the diagnosis of mood and behavioral disorders may be made before a first epileptic seizure. This bidirectionality suggests that structural and functional modifications of one disease increase the risk for the development of the other. In this review, we included the most recent articles concerning the terms "mental disorders", "epilepsy", and "risk factors" in *PubMed*. Book chapters were also referred for this work. We gave preference for population-based studies, especially those with more than 100 patients studied.

KEY WORDS: epilepsy, comorbidity, mental disorders, risk factors, physiopathology

1. INTRODUCTION

Ian Curtis, the famous Joy Division band's vocalist and song writer had a transient personality. He could show different behaviors at different times and with different people. Sometimes he was angry and spiteful, but more often was compliant and kind. He was diagnosed as epileptic when he was 23 years old. His fits varied in frequency and intensity, and anticonvulsant medication, which he took regularly, seemed to make his mood swings more radically. His frenetic style on stage simulated his own real epileptic seizures. Ian Curtis killed himself at his home in Macclesfield, England. He was 24 years old. The history of his life was recently portrayed in the movies "Control", launched in 2007. [1]

This case exemplifies how an epileptic disorder can transform people`s lives in true tragedies, harming their quality of life, changing personality traits and eventually increasing malady and causing death. Epilepsy is quite common also in "anonimous" individuals, and comprehension of its comorbidities, especially those pertaining to the psychiatric sphere, is a basic element for its management.

Epilepsy is a frequent neurological disorder with a worldwide distribution, although most people with epilepsy (PWE) live in underdeveloped countries. The term *Epilepsy* comprises many conditions typified by a tendency to spontaneous recurrence of epileptic seizures. Epilepsy occurs in all ages and can be associated to several cognitive, social and psychiatric troubles. [2]

Epileptic seizures are clinical expressions (symptoms) that begin abruptly and have a great variability in presentation form. A seizure can present with motor, sensorial, autonomic and/or state of consciousness changes. [3] The common physiopathological substrate for all types of epileptic seizures is a

disequilibrium between excitatory and inhibitory influences on settled neuronal pathways. In summary, there is a state of hyperexcitability supplied by predominant excitatory strengths. Epilepsies and epileptic seizures are divided in generalized (when neuronal hyperexcitability originates in both cerebral hemispheres simultaneously) and focal (localized unilateral neuronal hyperexcitability). [4, 5]

The most common epileptic disorder is the Temporal Lobe Epilepsy (TLE), which afflicts 40% of adult PWE. [6] Temporal lobe seizures belong to three distinct types: simple partial (aura only), complex partial (most commonly absences with automatisms), and secondarily generalized. TLE is divided in mesial (onset on hippocampus and amygdala) and lateral (onset on temporal neocortex). Mesial TLE has high indices of association with psychiatric disorders, because it involves the Lymbic System, the main integrator of emotional processes. [7, 8] The most common pathology causing mesial TLE is hippocampal sclerosis. [3]

The epileptic seizure temporally subdivides the clinical state of the PWE into two distinct periods of time: ictal (or peri-ictal) and interictal (when there isn't any sustained-release excessive rhythmic neuronal discharge). The essential focus of pharmacologic treatment of epilepsy is the hamper of ictal phenomenon. In general, this is achieved in about two thirds of cases. [2] Nevertheless, study of the interictal condition of PWE is also very important, and has improved the comprehension of epileptic phenomenon as a whole.

One of the most important issues not linked to the pharmocological control of seizures is the assessment of comorbidities in PWE. These patients have an increased risk for cognitive, behavioral, and psychosocial disorders. [8,

9] By the way, not only a poor control of seizures, but also the presence of comorbidities may directly affect quality of life of PWE. There is an increased risk for suicide in PWE, compared to the general population, and this risk is even greater in patients with a history of a psychiatric disorder, especially with the association between depression and anxiety. [10]

Epilepsy associated with mental disorders is a condition already known since Antiquity. Most part of stigma that follows PWE is descendent from the assignment of supernatural entities, like gods, witches, and devils, to the epileptic disorder. [11]

Prevalence of the association of epilepsy and psychiatric disorders ranges from 20 to 50%, reaching 80% in selected populations, like individuals with TLE, and medically intractable patients, candidates to surgical treatment. These indices are far superior to those found in general population (10-20%). Differences in methods of investigation and in populations studied are the main contributory factors for variable results. Also distinct epidemiological definitions (punctual prevalence, cumulative prevalence, lifelong prevalence), with their proper meanings, may contribute equally to variability of results. [12,13]

Risk factors for the main psychiatric comorbidities in PWE (depression, anxiety and psychosis) are classified in (1) neurobiological, (2) psychosocial, and (3) pharmacological factors. Major neurobiological factors are: type, frequency, duration, age of onset, and lateralization of epileptic seizure, genetic predisposition, gender, and presence of structural lesion. Issues concerning surgical treatment of epilepsy, like lateralization, type of resection, histopathological diagnosis, and surgical prognosis have been studied also. Other factors like hippocampal volume loss, temporal and frontal lobe glucose

hypometabolism, and neurotransmitter and hormonal substances changes, may also be highlighted. As psychosocial factors we could name the "learned despair", restraints to normal daily living activities, low self-esteem, educational and Professional difficulties, stigmatization, and social rejection. Among pharmacological factors, adverse effects of central nervous system (CNS) depressor antiepileptic drugs (DAEs), withdrawal of a mood stabilizer drug, polytherapy, starting a new DAE, and dose adjusting have been cited. [14,15]

There is a heterogeneous association between epilepsy subgroups and psychiatric disorders. In most patients, several chronic and acute risk factors can be identified. These factors are difficult to study retrospectively, and establishment of a cause and effect relationship may not always be possible. Literature data is highly controversial, and there is a huge difficulty to compare studies, because of the great variability in definition of essential terms like "epilepsy", "psychiatric disorder", and the proper explored risk factors.

It is important to highlight that there isn't a unidirectional relationship between epilepsy and mental disorders, namely, not only the epileptic disorder can antedate settlement of psychiatric symptoms in a given patient, but also the diagnosis of mood and behavioral disorders may be made before a first epileptic seizure. This bidirectionality suggests that structural and functional modifications of one disease increase the risk for the development of the other. [16]

There is increasing evidence that both in epilepsy and in mental disorders, changes in interaction between serotonergic and noradrenergic neurons with glutamatergic systems are associated to abnormal neuronal circuitries and hyperexcitability. This hyperexcitability could evoke both seizure

activity and emotional dysfunctions. [15] Furthermore, decrease in synaptic levels of neurotransmitters, as well as elevation in glucocorticoid levels could influence intracellular signaling pathways, like cyclic Adenosine Monophosphate (cAMP), and originating disorders of neurotrophic factors, like Brain-Derived Neurotrophic Factor (BDNF). [17, 18]

Therefore, the association between TLE and psychiatric disorders seems to be highly prevalent. This comorbidity affects directly clinical prognosis of the epileptic seizures, and also the quality of life of the patients with this type of epilepsy. It appears that there are common physiopathological mechanisms in both TLE and mental disorders, in general affecting neuronal circuitries of Lymbic System. Genetic disorders, like polymorphisms of receptor genes of many neurotransmitters, and also of neurotrophins, like BDNF, might be involved in this association.

In this review, we included the most recent articles concerning the terms "mental disorders", "epilepsy", and "risk factors" in *PubMed*. Book chapters were also referred for this work. We gave preference for population-based studies, especially those with more than 100 patients studied.

2. CONCEPTS IN EPILEPSY

The term Epilepsy comprises several syndromes which the main characteristic is an enduring predisposition to recurrent non-provoked epileptic seizures. [2] Epileptic seizures are sudden and brief attacks of altered consciousness, motor, sensitive, psychic, cognitive or autonomic dysfunctions, or an inappropriate behavior, caused by excessive or synchronic abnormal neuronal activity in the brain. [3]

The epilepsies and epileptic seizures are classified in focal and generalized. [4,5] Regarding focal epilepsies, the seizure clinical expression is determined by the topographical localization of the neuronal discharge, as well as its extent of spread in the brain. For the sake of conceptualization and pre-surgical neurophysiologic assessment of epilepsies, the region that yields the neuronal discharge is named Ictal Onset Zone, and the regions that generate the seizure's clinical features are named Symptomatogenic Zones. This is an important distinction, because the region where the discharge starts is not always able to produce clinical manifestations ("silent cortex"). In this case, surgical removal of the symptomatogenic zone would not be curative, because the real source of the epileptic disorder would not be included in the removed tissue. [19] The physiopathology of generalized seizures is diverse, depending on a genetically-determined thalamocortical circuitry dysfunction. [20]

Regarding etiology, epilepsies are divided in idiopathic (without structural brain lesion), symptomatic (with a structural lesion seen in neuroimaging exams) and cryptogenic (with a presumable etiology, not diagnosed at all). [5]

Estimated incidence of epilepsy in developed countries is about 50/100,000/year [21], and these numbers may double in poor countries. [22] In general, we find a bimodal distribution, with peaks of incidence in the first year of life and after 60 years of age. Prevalence of active epilepsy in most regions of the world is in turn of 5-10/1,000, although it may be even greater in some localized areas. [23,24] General prognosis for complete seizure control is good, since 70% of patients acquire remission after five years of diagnosis.[25, 26] Nevertheless, both adults and children with epilepsy an increased risk for death, when compared \with normal individuals. [27, 28]

3. TEMPORAL LOBE EPILEPSY

Temporal lobe epilepsy represents most patients with symptomatic or cryptogenic focal epilepsies. Types of seizures in TLE include simple partial, complex partial, and secondarily generalized seizures. Seizures most often originate in amygdalo-hippocampal region, in the medial and basal portion of temporal lobe. Hence, mesial temporal epilepsy (MTE) is the most frequent focal epilepsy. [29-32]

In MTE, seizure begins in more than 90% of the cases with an unnatural rising epigastric sensation. Other autonomic, psychic (i.e.: fear) and sensitive (i.e.: olfactory sensation) symptoms could occur also. Complex partial seizures of MTE almost always implicate motor arrest or automatisms (oroalimentary or gestural), early in the course of seizure. Ictal features with lateralizatory value include: dystonic posture of one superior limb (contralateral to the epileptic focus), early shift of the head (ipsilateral), late version of head, on transition to secondary generalization (contralateral). Intelligible vocalizations suggest onset of seizure in the non-dominant hemisphere. Most often, temporal lobe seizures last about two minutes, and are followed by a post-ictal confusional state. Post-ictal aphasia suggests seizure activity in the dominant hemisphere. MTE is the most common medically refractory focal epilepsy, and also one of the most surgically treatable. [33]

Lateral (neocortical) TLE is less frequent, and generally is characterized by an auditory aura. [34] Most often, seizures yielded in the lateral portion of temporal lobe are shorter in duration. Vertiginous hallucinations were described with temporo-parietal discharges.

Most frequently structural lesions associated with TLE are: hippocampal sclerosis, benign tumors (i.e.: ganglioglioma, neuroepithelial dysembrioplasic tumors), vascular malformations (i.e.: cavernoma), and malformations of cortical development (i.e.: focal cortical dysplasia). Hippocampal sclerosis coexisting with an extratemporal lesion is called dual pathology, a condition that carries a greater degree of difficulty for diagnosis, and worst prognosis. [35]

Considering the importance of limbic circuitries for the neuropsychiatric diseases, it is not a surprise the observation that many patients with TLE present concomitant psychiatric disorders, like depression and anxiety. [36]

4. COMORBIDITIES IN EPILEPSY

The term comorbidity refers to a more than occasional concomitant presence of two medical conditions in the same individual. [37] Comorbidity does not implies directionality or a cause-and-effect relationship, and diseases may coexist randomly, or also share common genetic and/or environmental mechanisms. [9] Epilepsy is frequently associated to cognitive, psychiatric or social troubles. [38]

5. PSYCHIATRIC COMORBIDITIES IN EPILEPSY

a. Historical

Association between epilepsy and psychiatric disorders has been described since the beginnings of Neurology and Psychiatry practices, and there are many examples found in literature. Hippocrates, about 400 b.c., observed a dichotomy between epilepsy and melancholia, and purposed that

these two entities could be linked by a probable common physiopathological mechanism. [11]

The history of the epilepsy-psychiatry interface had its beginning imprinted by the empirical association of these conditions with gods, witches, devils, and supernatural phenomena. The Greeks referred to epilepsy as the "sacred disease". In those years, Hippocrates that rush of fury that led Hercules to kill his children had an epileptic nature. The Romans referred to epilepsy as "morbidus lunaticus", related to the different phases of the moon. In the Arabic world, the epilepsy-mental disorders-devils association persisted, and prophets, like Mohammed and Saint Paul, that periodically heard voices and fell on the floor, supposedly had epilepsy. [39]

In the XIXth century and in the beginning of the XXth century, epilepsy was a common diagnosis in asylums housing patients with mental disorders. The most sicker individuals were treated by psychiatrists, whereas those with less severe pictures stayed in the community, where they were treated by general physicians or neurologists.[40]

In the 1920's decade, Emil Kraepelin made observations that are considered the basis for the modern psychiatric diagnostic classification. Kraepelin described precisely the affective changes of PWE, years before the age of electroconvulsive therapy. Dysphoric events, characterized by irritability, with or without bursts of fury, were considered by him the most frequent psychiatric disorder in PWE. Depression, anxiety, headache, and insomnia were very frequent complementary symptoms, although euphoric mood was less common. [41]

Heinrich Landolt identified different types of of psychotic episodes and their correlations with epileptic seizures and the electroencephalogram (EEG), introducing the concept of "Alternant Psychosis or Forced Normalization".[42] His work was later complemented by Slater and Beard, with the article "Schizophrenia-Like Psychosis of Epilepsy", where it was purposed an agonic relation between epileptic seizures and psychotic states. [43]

More recently, the introduction of advanced techniques of neuroimaging, like Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and the spectroscopy, combined with animal models and refined behavioral tests, made it possible the identification of common physiopathological mechanisms to both the epilepsies (especially TLE) and psychiatric disorders (especially major depression).

b. Epidemiology

There are few community-based studies on prevalence of psychiatric conditions in PWE. Most of these studies involve specific epileptic populations, in tertiary centers for attention to PWE. Community-based epidemiologic studies suggest a lifelong prevalence of psychiatric disorders in PWE, both adults and children, between 20 and 50%. [13, 44-52] Recently, Tellez-Zenteno et al. using data from the Canadian Community Health Survey, with administration of the World Mental Health Composite International Diagnostic Interview (CIDI), found a lifelong psychiatric disorder diagnosis in 35% of PWE, compared with 20% of non-epileptic individuals. [9]

The great variability of results obtained has been ascribed to differences in the methodology applied and in populations studied. It is well known that

psychiatric pathologies could be overrated in selected populations, like TLE or refractory patients [53], in whose prevalence of mental disorders may reach 80%. [54]

       c.   Methods of psychiatric assessment

Psychiatric assessment can be made basically by two types of interviews: structured interviews and self-applicable questionnaires (non-structured). [12] Non-structured interviews have been progressively replaced by structured interviews in the last years, to obtain a greater diagnostic accuracy. Structured interviews are composed by a set of key questions intending the fulfillment of well-defined diagnostic criteria included in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Main representatives are the Structured Clinical Interview for DSM Disorders (SCID) [55] and the Mini-International Neuropsychiatric Interview (MINI). [56] Self-applicable questionnaires, like the Beck Depression Inventory (BDI) [57], and the Center for Epidemiologic Studies Depression Scale (CES-D) [58], in general are less extensive and are based upon subjective criteria. Results obtained by self-applicable tests tend to be overrated regarding prevalence of psychiatric disorders.

Nevertheless, studies of lifelong prevalence of psychiatric disorders in PWE point to upper indices, compared to those found in general population. [59] For a comparison between several studies, see Tables 1e 2 In community-based studies (Table 1), prevalences varied between 5.9% e 54.5%. Only one study (Davies et al.) used structured interview for psychiatric diagnosis. This study found a superior number (37%), compared with other older population-

based studies that used unstructured interviews. Regarding studies of selected populations (performed in tertiary centers, in general as part of a pre-surgical evaluation), prevalence varied between 6.7% and 80%. Clearly, patients with difficult-to-control seizures, and especially those studied with structured interviews, trend to show increased frequencies of psychiatric comorbidities.

d. Risk factors

Many papers have been demonstrated that patients with TLE have an increased risk for psychiatric disorders, when compared to patients with other non-neurological chronic diseases. [7, 38, 54, 60] Notwithstanding, it is still controversial if patients with TLE have increased risk for development of a mental disorder when compared with patients with other types of epilepsy. Two important studies didn't find any differences in the risk of patients with TLE, focal extratemporal, and idiopathic generalized epilepsies.[61, 62] It is possible that greater prevalence of psychiatric disorders in patients with TLE could depict just the dominant prevalence of TLE related to other epilepsies.[63]

Despite this conjecture, it is plausible to believe that the same neuronal circuitries involved in the physiopathogenic mechanisms of TLE are also responsible for the production of psychiatric symptoms.[15] Purposed mechanisms for this frequent association could be arbitrarily divided in clinical, biological and environmental causes. Regarding clinical factors, it has been enrolled: number of epileptic seizures since onset of disease, effects of antiepileptic drugs, lateralization of the epileptic focus, gender and psychiatric familial history. [8]

Biological factors concern chemical and structural changes in the Lymbic System circuitry, the site of processing of behavior and emotions. [14] Environmental factors possibly involved with psychiatric comorbidities in epilepsy include: loss of independence, social stigma, financial and legal restraints (i.e.: driving license). [64] In a prospective study achieved in the New York University, Devinsky et al. assessed the impact of several clinical variables on the quality of life of patients with intractable epilepsy, in pre-surgical evaluation. Presence of depression, assessed by the BDI, was the only predictive factor for achievement of low indices of quality of life, assessed by the Quality of Life in Epilepsy (QOLIE-31) survey. Neither other factor (frequency of seizures, localization, age, gender, marital status, duration and type of seizure, or number of DAE) was predictor for quality of life. [65]

PWE have a significantly increased risk for suicide related to general population. Two big studies, made in Canada [9] and Denmark [10], showed that PWE has 2 to 3 times more risk of suicide than control individuals. Danish study found a risk of suicide even greater between epileptic patients with a specific comorbidity: mood disorder plus anxiety.

6. SPECIFIC PSYCHIATRIC DISORDERS

a. Mood disorders

Main neurobiological risk factors for depression in PWE that has been studied are: lateralization of epileptic focus, frontal lobe hypometabolism, and hippocampal volume.

Regarding lateralization, Hurwitz et al.[66] found association between left-sided epileptic focus and depressive mood. In this study, seizures yielded

by the right hemisphere were followed by laughter and seductive behavior. As a seizure activity localized in one hemisphere probably "releases" the opposite hemisphere, the authors postulated that the dominant hemisphere could be responsible for negative emotional states, and the non-dominant hemisphere could yield the opposite effect. Other theory hypothesizes that a seizure activity in the non-dominant hemisphere could result in neglect of negative emotions. [63] Many controlled studies comparing seizure focus with degrees of depression found increased frequencies of depression with a focus in the left hemisphere, independent of seizure type. [67-70], although other studies didn't ratify this correlation. [71] A complex interaction between several factors would be employed in this association.

Recent works using PET and SPECT have shown an association between epilepsy and frontal lobe dysfunction with hypometabolism. Bromfield et al.[72] studied 23 patients with complex partial seizures, candidates for surgery, regarding depressive features (BDI > 11), compared to normal controls. Patients with a left-sided temporal focus presented more depressive symptoms as well as a bilateral inferior frontal lobe hypometabolism. Victoroff et al.[70] studying 53 epileptic patients candidates for surgical treatment, observed that an ictal onset on the left was associated to an increased frequency of depression (79% x 50%, non-significant). It has not been found any correlation between current affective state and metabolism in the frontal lobes, but it was interesting to observe that a history of depressive episodes (identified by SCID) significantly correlated with a left frontal lobe hypometabolism. Hermann et al. didn't find any correlation between humor and laterality, but a left-sided focus was significantly associated to the severity of frontal dysfunction (measured by

Wisconsin Card Sort Test) and dysphoria.[73] Contrarily, a right-sided focus was inversely associated to frontal dysfunction and dysphoria (non-significant results).

Our group studied 97 patients with TLE regarding risk factors for affective disorders. [74] A positive family history of psychiatric disorders (O.R. = 3.8; p = 0.003) and interictal EEG epileptiform discharges involving the left temporal lobe (O.R. = 2.9; p = 0.041) were significantly associated with an increased risk for an affective disorder in population studied. This article reinforced the importance of biological factors, specifically genetic and anatomical substrates, for the development of humor disorders in PWE.

Few studies evaluated the association between hippocampal volume loss, depression and epilepsy. Quiske et al. found higher BDI scores in patients with TLE and hippocampal sclerosis, when compared to patients with normal MRI. [75] Another study also identified an association between higher scores for depression and increased volume of left hippocampus, in patients with right hippocampal sclerosis. [76] Also studies with PET showed an association between higher scores for depression in PWE with metabolic alterations in temporal lobes, compared to PWE with normal PET. [77]

b.   Anxiety disorders

The main types of anxiety disorders described in DSM-IV are: generalized anxiety disorder, panic disorder, phobia, and obsessive-compulsive disorder. The risk factors pointed for the association between epilepsy and anxiety are: frequency of seizures, surgical treatment for epilepsy, age, type of seizure, and perception of stigma. [78,79]

Frequency of seizures was associated to anxiety in some works [80, 81], but this is not an unanimity. [82] Studies combining PET with electrophysiological data indicate the right temporal lobe as the main structure responsible for pathogenesis of anxiety in epilepsy. [83] Probably, more than the frequency of seizures, fear of falling down or to die is the real critical factor for the development of anxiety in PWE. Surgical treatment for epilepsy may increase the frequency of anxiety disorders in these patients, especially those that experience a greater than 75% reduction in their seizures after surgery. [84]

Regarding age, minimal effects were observed, although a late onset of epilepsy could be associated with higher degrees of anxiety. [85] Risk for anxiety seems to be greater in focal epilepsies (especially TLE) than in generalized epilepsies. [86] Higher indices of anxiety were found in patients with poor pharmacological control of their seizures. [87,88] An important factor linked to anxiety in PWE is the stigma perception [89,90], and this factor is heavier in young patients. [83,91]

c.   Psychotic disorders

 Literature regarding risk factors for psychotic disorders in epilepsy is highly controversial, and most studies are restricted to interictal psychosis. [92]

 Regarding duration of epilepsy, in most series, time for the first psychotic manifestation from the onset of epilepsy is about 11 to 15 years, raising an etiological meaning to the epileptic disorder, through a mechanism "kindling-like". [40] TLE is the epilepsy most associated with psychosis in almost all case series. In a non-systematic revision of 10 studies, 76% patients suffering from psychosis had TLE. [40] Major criticism to these studies is that

their results may reflect just the higher prevalence of TLE in the community.

Severity of epilepsy is one of the most important risk factors for psychosis, and

it could be measured by duration and multiplicity of seizures, history of status

epilepticus, and poor clinical response to treatment. [40] Flor-Henry [93]

originally suggested that left temporal lobe dysfunction was a risk factor for

schizophreniform psychosis. Trimble's analysis of 14 studies with 341 patients

with TLE found that 43% had a left-sided epileptic focus, 23% on the right, and

34% had bilateral changes. [40] This data regarding laterality were supported by

neuroimaging studies, especially SPECT and MRI. Mellers et al.[94], using a

verbal fluency activation paradigm and SPECT, compared patients with

schizophrenia-like psychosis (n = 12), schizophrenia (n = 11), and non-

psychotic epileptic patients (n = 16). Psychotic epileptic patients showed and

increased blood flow in the superior temporal gyrus, during activation, related to

the other groups. Maier et al. [95] compared the amygdalo-hippocampal

volumes and hippocampal N-Acetyl Aspartate (NAA) (by spectroscopy) of

patients with TLE, with (n = 12) and without schizophreniform psychosis (n =

12), non-epileptic schizophrenics (n = 26), and normal individuals (n = 38).

Psychotic patients shoed significant reduction of NAA in the left temporal lobe,

with a more accentuated phenomenon observed in epileptic patients. PWE

showed bilateral volume reduction, whereas psychotic patients had a more

prominent atrophy of the left amygdalo-hippocampal complex.

Interictal psychosis seems to be different from schizophrenia, especially

because interictal psychosis courses with more affective symptoms and has a

better prognosis. Although hippocampal alterations could be related to both

disorders, bilateral increase of amygdales (with less volumetric changes in

hippocampi) is typical of interictal psychosis, suggesting a great difference between both conditions. This hypothesis was supported by a recent study, with 26 patients with epileptic psychosis, 24 non-psychotic patients with TLE, and 20 normal controls. Psychotic patients had significant bilateral increases of amygdales, in comparison with the other groups. These findings were not correlated with lateralization of the focus, and neither with the duration of epilepsy. [96]

7. PSHYSIOPATHOLOGY

a.   Bidirectional relation

It is demonstrated that some specific humor and behavioral disorders may show a bidirectional relation with the onset of epileptic seizures, namely, a psychiatric diagnosis may precede onset of seizures, especially in three situations: major depression, suicidal ideation, and Attention Deficit Disorder with Hyperactivity (ADDH).

Case-control studies [97,98] as well as longitudinal studies [99], in children, showed an increased risk of 2.5 fold for patients with a diagnosis of ADDH suffer a first epileptic seizure.

Three controlled studies assessed the temporal relation between depression and epilepsy. One population-based case-control study found a 7-fold increased risk for and adult with depression to develop epileptic seizures, compared to normal individuals. The risk increased to 17-fold with focal epilepsies. [49] Hesdorffer et al. [100] observed the same temporal relation between depression and a first seizure, with a 6-fold increased risk. Data from

these two studies were confirmed in a population-based controlled study, proceeded in Island, with 324 patients above 10 years of age, with a first non-provoked seizure or newly diagnosed epilepsy, and 647 controls: major depression, diagnosed after DSM-IV criteria, increased the risk for epilepsy in 1.7-fold. This same atudy showed that a suicide temptation is associated with a 3.5-fold increased risk for epilepsy. [16]

b.   Common physiopathologic mechanisms

This bidirectionality suggests a common underlying susceptibility to epilepsy and humor disorders. Literature is plentiful of studies on molecular and cellular biology and anatomy of the brain in both diseases. [101] Those mechanisms are strongly interconnected, and functional and structural alterations in one disease may give rise to the other.

i.   Animal models

One of the best studied models in TLE uses convulsant substances, like kainate and pilocarpine, in general, systemically injected. After induce a status epilepticus in the animal, in this model, it follows a period of latency along some weeks, with further development of spontaneous seizures. [102] Other experimental model utilized is the electrical kindling, but this method does not seem to reproduce the typical physiopathological events of TLE, compared to the pharmacological method. With kindling, seizures do not occur spontaneously, a hippocampal sclerosis does not develop, and there is no latency period between initial precipitant injury and the development of seizures.

Recently, Mazaratti et al. [103] investigated if a kindling-induced chronic increase of susceptibility to seizures could result in a depressive behavior in rats. Two to four weeks after application of 84 subconvulsant electrical stimuli (each five minutes) in ventral hippocampus of adult Wistar rats, the authors applied two tests: Forced Swim Test (FST) and a gustative test (preference for sugar). Immobility in the tank on FST is equivalent to depression, as the animal does not show any initiative to escape in a stress situation. The second test aims to reproduce the loss of ability to seek pleasure, a frequent symptom in depression. The study showed that rats submitted to kindling exhibited a significant increase in time of immobility on FST, associated to a loss of preference of sweet taste, compared to controls. The authors concluded that the alterations in neuronal plasticity caused by kindling would be followed by a depressive behavior.

The role of neurotransmitters in the physiopathologic mechanisms of humor disorders is recognized since some decades ago. [104] The roles of gama-aminobutyric acid (GABA) and glutamate in epileptogenesis were already demonstrated in several studies in animals and humans. The Genetically Epilepsy-Prone Rat (GEPR) provides an experimental model for both epilepsy and depression. In this model, mutated animals are highly sensible to auditory stimuli, to which they answer with generalized tonic-clonic seizures. Moreover, GEPRs show endocrinologic changes similar to those identified in depressive patients: increased corticosteroid plasmatic levels, decreased secretion of growth hormone, and hypothyroidism. [105] Defective arborizations of noradrenergic and serotonergic circuitries were observed in those animals. An increase in the levels of these neurotransmitters could prevent seizures,

whereas diminished levels have the opposite effect. [105] One classic study showed that fluoxetine, a selector synaptic serotonin reuptake inhibitor, provoked a dose-dependent reduction in the frequency of seizures in GEPRs, which correlated with extracellular thalamic serotonin concentrations. [106]

> ii.   Studies in humans

Animal serotonergic transmission was demonstrated in the brain of depressed patients [107, 108], the same feature found in studies with PET, in patients with TLE. [109, 110] In a more recent study, Hasler et al. compared the level of 5-HT1A receptor binding to a specific antagonist, in 37 patients with TLE, with and without major depression (diagnosis by SCID), using PET. Beyond a decreased binding to 5-HT1A receptors in the epileptic focus, patients with major depression exhibited a more extensive reduction in binding, involving non-lymbic areas, distant from the epileptic focus. [111]

One of the most important proteins involved in the functioning of Lymbic System is the BDNF. This element may influence both neuronal electrical activity and memory and behavior functions, which are directly related to hippocampus in its connections. Changes in BDNF are associated to hippocampus atrophy, alterations in memory, and temporary amygdalar hypertrophy, with alteration in fear process. Moreover, studies with PET suggest a glucose hypometabolism in temporal and frontal lobes in the TLE-depression association. [112]

A functional polymorphism of *BDNF* gene, the Val66Met, has been studied as a predisposition factor for many neurological and psychiatric disorders, with variable results. Regarding epilepsy, it seems that there isn't any

direct relation with the polymorphism. [113] Notwithstanding, depression, anxiety, psychosis and eating disorders have been often associated to the presence of Val66Met polymorphism in the *BDNF* gene. [112] A recent meta-analysis affirmed the association of Val66Met to substance-related disorders, eating disorders, and schizophrenia. [114]

Our group also studied the association between 5HTTLPR and 5HTTVNTR allele variants in serotonin transporter gene and epileptogenesis in TLE. We compared 175 patients with TLE and 155 healthy control individuals, and observed an association between the presence of 5HTTLPR and 5-HTTVNTR less transcriptional efficient combined genotypes and TLE. Our results agreed with several other studies showing that low transcriptional activity 5-HTT genotypes are associated with neuropsychiatric disorders, such as depression, suicidal behavior, attention deficit hyperactivity disorder, and personality disorder. [115]

8. DISCUSSION

There is a growing evidence for psychiatric comorbidities in epilepsy. Studies on prevalence have demonstrated advances in methodological issues, improving reliability of results. Future research need to focus on physiopathologic mechanisms, especially regarding functional and structural alterations involving human neuronal circuitries in the Lymbic System. Although many studies on a possible association between epilepsy and the polymorphism of the *BDNF* gene, Val66Met, did not find any positive result, a strong evidence exists linking this polymorphism to psychiatric disorders. Likely,

serotonin allelic variants may also influence the modulation of serotoninergic

system, and eventually epileptogenesis in TLE. For those reasons, it remains

plausible to continue researching genetic variants in this field.

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TABLES

Table 1 – prevalence of psychiatric comorbidities in PWE. Population-based studies.

AUTHORS	N	INSTRUMENT	POPULATION	PSYCHIATRIC DISORDERS	MOOD DISORDERS	ANXIETY DISORDERS	PSYCHOSIS	SUBSTANCEE ABUSE
Pond and Bidwell, 1960 UK	245	Unstructured psychiatric interview	Children with epilepsy – community-based	29%	-	-	-	-
Gudmundsson, 1966 Iceland	654	Clinical interview (unstructured)	Epilepsy (community-based)	54.5%	-	-	9%	-
Graham and Rutter, 1970 UK	63	Unstructured psychiatric interview	Children with epilepsy – community-based	28.6%	-	-	-	-
Forsgren, 1992 Sweden	713	Chart review (unstructured)	Epilepsy – community-based	5.9%	-	-	0.7%	-
Bredkjaer et al., 1998 Denmark	67	ICD-8	Epilepsy – community-based	16.8%	-	-	-	-
Hackett et al., 1998 India	26	ICD-10	Epilepsy – community-based	23.1%	-	-	-	-
Davies et al., 2003 UK	67	SCID	Epilepsy – community-based	37%	-	-	-	-
Ettinger et al., 2004 USA	775	CES-D	Epilepsy – community-based	-	36.5%	-	-	-
Strine et al., 2005 USA	427	Kessler 6 scale	Epilepsy – community-based	-	32.6%	14.4%	-	-
Kobau et al., 2006 USA	131	Health Style Survey (self- reported depression and anxiety)	Epilepsy – community-based	-	39%	39%	-	-

| Tellez-Zenteno et al., 2007 Canada | 253 | CIDI | Epilepsy – community-based | 23.5% | 17.4% | 12.8% | - | - |

Table 2 – Prevalence psychiatric comorbidities in PWE. Studies in selected populations.

Victoroff, 1994 USA	60	SCID – DSM-III-R	TLE – candidates for surgery	70%	58.3%	31.7%	13.3%	-
Edeh and Toone, 1987 UK	88	CIS	Epilepsy – selected by general practitioners (GP)	48%	22%	15%	3.4%	-
Gaitatzis et al., 2004 UK	5834	ICD-9	Epilepsy – selected from a database generated by GP	41%	18.2%	11.1%	9%	2.4%
Mensah et al., 2006 UK	499	HADS	Epilepsy – from GP	-	11.2%	-	-	-
Perini et al., 1996 Italia	38	SADS, BDI, STAIX1, STAIX2	JME and TLE (selected) patients	80% (TLE), 22% (JME)	55% (TLE), 17% (JME)	15% (TLE), 11% (JME)	-	-
Swinkels et al., 2001 Netherlands	209	CIDI	Epilepsy – tertiary epilepsy center	-	24.9%	29.7%	0.5%	20.1%
Havlová, 1990 Czech Republic	225	Chart review (unstructured)	Cohort of epileptic children	6.7%	-	-	-	-
Stefansson et al., 1998 Iceland	241	ICD-9	Epileptic patients receiving benefits	35.3%	-	-	6.2%	5%
Jalava and Sillanpaa, 1996 Finland	94	Chart review and ICD-9	Epilepsy – selected from different sources	24%	-	-	3.1%	-
Gureje et al., 1991 Nigeria	204	CIS	Epilepsy – tertiary center	37%	-	-	30%	-
Araújo Filho et al., 2008 Brazil	270	SCID	Refractory TLE and JME from a tertiary epilepsy center	50% (TLE), 49% (JME)	25.8% (TLE), 19% (JME)	14.1% (TLE), 23% (JME)	15.8% (TLE), 3% (JME)	2% (JME)
Bragatti et al., in press Brazil	98	SCID	TLE – selected from a tertiary epilepsy center	54.1%	42.9%	18.4%	6.1%	6.1%

9.2. ARTIGO nº 2

Prevalence of Psychiatric Comorbidities in Temporal Lobe Epilepsy: Value of Structured Psychiatric Interviews

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ABSTRACT

Background**:** Although many studies have demonstrated a great prevalence of psychiatric disorders in epileptic patients, most have used unstructured psychiatric interviews for diagnosis. This approach might lead to significant differences in results observed. Here we present a study evaluating the prevalence of major psychiatric comorbidities in a cohort of Southern Brazilian patients with temporal lobe epilepsy using a structured clinical interview.

Methods**:** We analyzed 98 patients (39 men and 59 women) with temporal lobe epilepsy regarding neuropsychiatric symptoms. Patients` mean age was 43 years old, and mean duration of epilepsy was 25 years. Patients were diagnosed according to the ILAE Classification of Epileptic Syndromes using clinical, EEG, and neuroimaging criteria. All patients were submitted to the Structured Clinical Interview for DSM-IV (SCID).

Results**:** Fifty-three patients (54.1%) presented major psychiatric comorbidities. Mood disorders were observed in 42 patients (42.9%), the most common being neuropsychiatric disorders. Anxiety disorders were the second most frequent disorders, observed in 18 patients (18.4%). Psychotic disorders and substance abuse were observed in 6 patients (6.1%) each. There were no clinical variables regarding epilepsy characteristics (age of onset, duration, response to antiepileptic drugs), and no MRI features associated with psychiatric disorders. Involvement of left hemisphere in EEG interictal abnormalities increased in 7 times the risk for mood disorders in our patients.

Conclusions**:** Our results are high, but similar to those observed in other studies that used similar structured interviews in populations of epileptic patients

attended at tertiary centers. The wide variation in percentages is probably attributable to the different patient groups investigated and to the even greater variety of diagnostic methods. Structured psychiatric interviews might contribute to a better evaluation of the real prevalence of psychiatric comorbidities in temporal lobe epilepsy.

INTRODUCTION

Epilepsy is a common neurological disorder. The world prevalence of epilepsy is estimated to range from 0.5 to 1.5% (Sander 2003). The term Epilepsy encompasses different neurological disorders characterized by a tendency to recurrent epileptic seizures. Epileptic seizures are the clinical correlates of paroxysmal events generated by an enduring condition of hyperexcitability and hypersynchrony of brain electrical activity. However, the clinical spectrum of epilepsy encompasses many neurobehavioral comorbidities (Elger and Schmidt 2008). Epilepsy and neurobehavioral conditions might share some physiopathologic, genetic, and environmental, mechanisms (Gaitatzis et al. 2004, Hermann et al, 2008).

The association between epilepsy and psychiatric disorders has been known since ancient times, but the last two decades were marked by an explosion of studies about this issue (Devinsky 2003). Prevalence of psychiatric comorbidities ranges from 20 to 40% in patients with epilepsy. In selected populations prevalences may reach two-fold higher values (Pond and Bidwell 1960, Silberman et al. 1994, Perini et al. 1996, Blumer et al. 1998, Davies et al. 2003, Swinkels et al. 2005, Tellez-Zenteno et al. 2005). Different definitions of psychiatric comorbidities, different study populations, and, the most important, different forms of psychiatric evaluation are factors that might explain the variability found. Studies with structured psychiatric interviews are still lacking.

The objective of the present study was to determine the prevalence of major psychiatric disorders in a cohort of patients with TLE living in Southern Brazil using a structured psychiatric evaluation, and compare the findings with studies conducted around the world. Moreover, we believe that our study is relevant

because it might contribute to a better view of the worldwide prevalence of psychiatric comorbidities in epilepsy.

METHODS

We studied a cohort of 98 consecutive Caucasian patients (59 women and 39 men) with TLE, from march of 2007 to december of 2008. Patients were selected from the Epilepsy Outpatient Clinic of Hospital de Clinicas de Porto Alegre, a tertiary hospital located in the Southern region of Brazil. Porto Alegre is the capital of Rio Grande do Sul state. The city has a population of 1,416,735, mostly composed by European immigrants (Portugueses, Germans, and Italians), distributed in an area of 496.8 km^2. The annual per capita income is U$ 4840.91 (IBGE Cidades@ 2009). Its economy is based on industry, commerce and services. In Brazil, health is the responsibility of the state and its access is universal. As in the rest of the country, health, education and safety are provided by both public and private services. It is estimated that about 2/3 of the population uses the governmental services.

Inclusion criteria for the study were presence of electroclinical and neuroimaging features of TLE, according to the ILAE classification for epileptic seizures and syndromes (Commission 1989, Maillard et al. 2004, Pascual 2007). Patients less than 18 years old of age, those with generalized epilepsies, extratemporal epilepsies, mental retardation (IQ scores below 70), brain tumor, systemic disease (ex.: systemic erythematous lupus, AIDS), or penetrating head trauma were excluded.

After giving written informed consent, all patients were submitted to the Structured Clinical Interview for DSM-IV (SCID) (First et al. 2001), divided into

six modules, for the detection of one or more lifetime diagnoses of the Axis I Diagnostic and Statistical Manual, fourth edition (DSM-IV) (American Psychiatric Association 2000). Interictal spikes were independently reviewed by two board-certified electroencephalographers (J.A.B. and C.M.T.) that were blind to psychiatric evaluation. Whenever the results were discordant, EEGs were reviewed by the two examiners together to reach a consensus. When available, all MRI exams were reviewed to improve etiological diagnostic. Control of seizures was assessed by an events calendar fulfilled by the patient. Seizures occurring more than once monthly were considered uncontrolled. Data regarding prior and current antiepileptic treatments, as well as the use of any psychotropic or sedative drug (ex.: antidepressants, antipsychotics) were registered in a database for posterior statistical analyses.

Results were displayed in a percentage form. We analyzed the impact of psychiatric diagnosis on main aspects of TLE (control of seizures, interictal EEG, MRI abnormalities, presence of aura). We compared results of patients with and without a positive SCID, regarding those aspects, using Pearson's chi-square test. All results are expressed using O.R. (95% C.I.). A significant level was considered when $p<0.05$. The study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre.

RESULTS

Mean age of the study population was 43.3 (± 12.3) years (range: 20 to 75 years), with a mean age at first seizure of 18.1 (± 14.3) years (range: 3 months to 67 years) and a mean duration of epilepsy of 25.3 (± 12.9) years (range: 2 to 51 years). The main clinical characteristics of the study population are shown in

table 2. Fifty-three patients (54.1%) had a diagnosis of at least one lifetime psychiatric disorder. Forty-two of the SCID-positive patients (42.9%) had a mood disorder; 18 (18.4%) had an anxiety disorder; 6 (6.1%) had a psychotic disorder, and 6 patients had alcohol or drug abuse (*table 2*). An association between mood and anxiety disorders was the most common psychiatric comorbidity observed, being present in 22 patients (41.5%).

Major depression was the most frequent mood disorder observed in our series, being present in 57% of the patients with mood disorders and in 25% of all patients. Dysthymic disorder was observed in 19% of patients with mood disorders (8% of all patients). A past depressive episode was observed in 14% of patients with mood disorders and in 6% of the total patient series. Generalized anxiety disorder was present in 5 patients (28% of patients with anxiety disorders and 5% of all patients), and panic disorder in 6 (2 with agoraphobia). Post-traumatic stress disorder was observed in 3 patients (*table 2*).

In *table 3* we present our findings compared with other reports with different methodologic characteristics. The overall prevalence of psychiatric disorders in our patients was 54%, with a pattern of dominant mood disorders occurring at two-fold higher rates than those for anxiety disorders. These values are high, but similar to those observed in other European or South American studies that used similar structured interviews in populations of epileptic patients attended at tertiary centers (Edeh and Toone 1987, Araújo Filho 2008). Moreover, we found a greater prevalence of psychiatric disorders in our patients when compared with the general population of Porto Alegre, data published in a previous study (Almeida-Filho et al 1997) (*table 4*).

Although there was a tendency to patients with uncontrolled epilepsy present some lifetime psychiatric disorder, we did not have found any statistical difference between patients with and without lifetime psychiatric disorders, regarding presence of MRI abnormalities, interictal EEG features, control of seizures, or presence of aura (*table* 5).

EEG and MRI features were analyzed separately searching for risk factors for psychiatric disorders in TLE patients. We categorized EEG data in right-only, left-only, and bilateral interictal temporal discharges. Involvement of left side (dominant hemisphere) was significant for lifetime mood disorders in TLE patients, with a risk of 7.1 (p=0.007). Less than half of our patients had MRI scans (n=43). There was no association between presence (uni or bilateral) or absence of hippocampal sclerosis with lifetime psychiatric disorders, or specifically depression, in our patients.

DISCUSSION

We observed a high prevalence of lifetime psychiatric disorders in our TLE patients. Psychiatric comorbidities were present in 54.1% of them. The main psychiatric diagnoses found in our series (*table 2*) were mood disorders (found in 42 patients, 42.9% of the total), followed by anxiety disorders (18 patients, 18.4% of the total). Psychotic disorders and substance abuse were observed in 6 patients (6.1%) each.

Our results agree with the literature. Most reports show that mood disorders are the most frequent psychiatric comorbidity in TLE patients (Kanner 2005, Schmitz 2005). According to previous reports, a higher prevalence of psychiatric comorbidities is observed in epileptic patients studied at tertiary centers (40-

60%) (Victoroff et al. 1994, Ring et al. 1998, Grabowska-Grzyb et al. 2006, Briellman et al. 2007), while population-based studies show an intermediate prevalence of about 20% (Edeh and Toone 1987, Jacoby et al. 1996, Ettinger et al. 2004, Mensah et al. 2006). Nevertheless, in all studies the frequencies of psychiatric disorders among epileptic patients were higher than in the general population (12.2-16.2%) (Kessler et al. 2003, Hasin et al. 2005, Patten et al. 2006).

Several authors have reported a wide variability of psychiatric comorbidities in epileptic patients. The prevalence of these comorbidities varies according to the type of patient studied, the type of psychiatric disorder studied, the duration of the study (last 12 months or lifetime), and the type of diagnostic procedure used (structured interview or self-applicable questionnaire) (Silberman et al. 1994, Perini et al. 1996, Blumer et al. 1998). For example, community-based studies of epileptic patients with structured interviews have found prevalences of psychiatric comorbidities ranging from 23.5% to 37.5%, always higher than in the general population (10-20%). In contrast, studies using ICD diagnoses and data from administrative registries have shown more varied results (ranging from 16.8 to 60%) (Pond and Bidwell 1960, Shukla et al. 1979, Jalava and Sillanpaa 1996, Bredkjaer et al. 1998, Hackett et al. 1998, Stefansson et al. 1998). The highest prevalences were found in populations extracted from lists of individuals with some other associated disease, and therefore probably with a selection bias (Pond and Bidwell 1960, Shukla et al.1979)

The prevalence of psychiatric disorders seems to increase according with the severity of neurological disorders, in the following sequence: patients with chronic non-neurological diseases, patients with non-epileptic neurological

diseases, patients with generalized epilepsies, patients with extratemporal focal epilepsies, patients with non-surgically treatable TLE, and finally, patients eligible for surgery (Manchanda et al. 1996, Glosser et al. 2000, Wrench et al. 2004). The prevalence of psychiatric disorders in TLE patients is, in general, two-fold greater than in the general population (Tellez-Zenteno and Wiebe 2008). Our data are closely similar to those observed in other selected populations of epileptic patients (Davies et al. 2003, Araújo Filho et al. 2008) Indeed, most of our patients (60%) do not have proper seizure control (*table 1*) (Almeida-Filho et al. 1997).

Another interesting aspect is the observation that studies conduced with structured interviews tend to point to higher frequencies of neuropsychiatric disorders in epilepsy (see *table 3*). Because the use of structured psychiatric interview is relatively more recent and limited to smaller populations, it is possible that larger epidemiological studies might underestimate the true prevalence of psychiatric disorders in epilepsy. Thus, further observations are necessary to clarify these matters.

We observed more than one type of lifelong psychiatric disorder in about 40% of our patients. Most frequently this association was between mood and anxiety disorders. This association has been recognized since ancient times, but its pathophysiologic mechanisms are still poorly understood (Temkin 1971). Studies with adults and children suffering from epilepsy have shown a high prevalence of this comorbidity in association with epilepsy, sometimes up to 70% (Jones et al. 2005, Kobau et al. 2006). Depression, anxiety and epilepsy seem to share some biological and structural mechanisms related to limbic

system dysfunctions. This is an interesting topic which has been intensely investigated over the last few years.

Fear is a frequent type of aura, been observed in about 15% of TLE patients (Devinsky et al. 1995), and sometimes mimics panic attacks (Kanner et al. 2004). A previous study (Strine et al. 2005) found a high prevalence of post-ictal anxiety symptoms in epileptic patients. However, we could not observe this association because there were too few patients with anxiety symptoms in our sample. Goldstein et al. (1999) observed an inverse correlation between seizure frequency and post-ictal anxiety symptoms. The authors suggested that this inverse association might be caused by "habituation" of the anxiety generator circuits (mostly amygdala) due to high seizure frequency, processing them as ordinary events. Another possibility could be that this inverse correlation would be due to the "learned helplessness" phenomenon (Hermann et al. 1996). Further researches are needed to clarify these aspects.

There are much evidence suggesting that TLE and depression may share common pathogenic mechanisms (Kondziella et al. 2007). For example, in both TLE and depression smaller volumes of frontal lobes have been found (Lavretsky et al. 2007, Mueller et al. 2007). High-resolution MRI studies have shown that hippocampal volumes in depression are decreased bilaterally (Sheline 2003) or in the left hippocampus only (Bremner et al. 2000). In TLE, volumes may be reduced on the site of seizure origin (Baxendale et al. 2005, Mueller et al. 2007) or, when combined with depression, bilaterally (Baxendale et al. 2005). Nevertheless, [1]H Magnetic Resonance Spectroscopy (MRS) studies revealed reduced glutamate concentrations in the anterior cingulate cortex in depressed adults (Auer et al. 2000) and children (Mirza et al. 2004). In

a study by Hasler et al. (2007) levels of glutamate/glutamine and GABA were also decreased in prefrontal dorsomedial and ventromedial regions. In TLE, most studies using interictal fluorodeoxyglucose-positron emission tomography (FDG-PET) have confirmed hypometabolism of epileptogenic temporal regions (Manno et al. 1994) such as the hippocampus (Semah et al. 1995), often bilaterally (Joo et al. 2004; Kim et al. 2006). Indeed, orbitofrontal hypometabolism of glucose has been suggested as a predisposing risk factor for the development of depression in patients with TLE (Salzberg et al. 2006). The relevant mechanisms may include extension of sclerosis and cell loss from the temporal lobe to extratemporal structures (Semah 2002) or compensatory neuronal inhibition (Salzberg et al. 2006). Alternatively, orbitofrontal hypometabolism may come secondary to depression or may just be a marker for general cerebral dysfunction associated with TLE (Salzberg et al. 2006). A strong hypothesis derived from these data, which needs further studies, is that neuronal hyperexcitability can possibly be expressed either as impaired emotions or seizure activity.

One limitation of our study was its inability to identify mood disorders not yet classified by DSM-IV (Krishnamoorthy et al. 2007). Another limitation of our study is its cross-sectional design which did not permit us to identify psychiatric disorders temporally related to seizures (peri-ictal and interictal symptoms). In these venues, mood disorders are different in epileptic patients when compared to subjects from the general population. There is an increasing recognition of an association between epilepsy and an affective-somatoform disorder named Interictal Dysphoric Disorder. The main symptoms of this provisional psychiatric diagnosis are temper and euphoria. Other less specific symptoms such as

depression, pain, insomnia, fear and anxiety, also compose this new entity (Blumer et al. 2004). Regarding psychotic symptoms, as is the case for mood disorders, there is also a common diagnosis in epileptic patients that is not listed in DSM-IV. This disorder has been named "alternate psychosis", a concept proposed by Tellenbach (1965) based on Landolt observations (1953), and typifies a genuine psychosis of epilepsy (POE) due to its close relation to epileptic activity. At times, ictal psychotic symptoms may be due to a focal nonconvulsive status epilepticus, with continuous subclinical epileptiform activity involving one frontal or temporal lobe (Schmitz and Trimble 2008). Post-ictal psychosis has a prevalence of about 7% in refractory epileptic patients (Tellez-Zenteno et al. 2007), especially when a double independent epileptic focus is present (Graham and Rutter 1970). Landolt observed a paradoxical EEG normalization in epileptic patients during the manifestation of psychotic symptoms, and called this phenomenon "Forced Normalization" (Landolt 1953). Finally, mood changes preceding (Blanchet and Frommer 1986) or following the epileptic event (Kanner and Balabanov 2002) are quite frequent. As ictal phenomena, however, depression (Taylor and Lochery 1987, Robertson 1992), and mania (Barczak et al. 1998, Humphries and Dickinson 1988), are much less frequent situations.

Although structured interviews are necessary for accurate determination of psychiatric diagnoses in epilepsy, their application in a busy clinical setting is not always feasible. Most rating scales and self-report questionnaires are developed to screen for psychopathology in nonepileptic patients. Nevertheless, validated screening instruments (such as The Mood Disorder Questionnaire and NDDI-E) were specifically developed to screen for the presence of psychiatric

disorders (especially mood disorders) in patients with epilepsy. These instruments are self-rating and can completed in a few minutes, and are confident, because they minimize the risk of overlap with adverse AED effects or preexisting cognitive problems (Hirschfeld et al. 2000, Jones et al. 2005, Gilliam et al. 2006).

CONCLUSION

We found a high prevalence of psychiatric disorders in our TLE patients. The most frequent diagnoses found were mood and anxiety disorders. Both conditions occurred simultaneously in 40% of patients. Our data agree with the international literature. In fact, the prevalence observed was more similar to those observed in European studies (*table 3*).This is interesting because our studied population is composed by descendent of Europeans. Thus, in spite of living in a different world region, it seems that psychiatric comorbidities in epileptics might remain similar to that observed in ancestor population. Our finding might suggest that genetic predisposing factors might be even more important that eventual environmental factors. This interesting aspect deserves further studies. Moreover, because of the high prevalence observed our data, our study agrees with growing evidence existing in literature indicating that TLE and psychiatric disorders share similar physiopathologic mechanisms.

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TABLES

Table 1 – Clinical features of the patients studied.

Factor		Number of patients (%)
Gender	Men	39 (39.8%)
	Women	59 (60.2%)
Controlled seizures	Yes	40 (40.8%)
	No	58 (59.2%)
Aura	Yes	64 (65.3%)
	No	34 (34.7%)
Family history of epilepsy	Yes	45 (45.9%)
	No	53 (54.1%)
Family history of psychiatric disorders	Yes	38 (38.8%)
	No	60 (61.2%)
Initial Precipitant Insult	Yes	24 (24.5%)
	No	74 (75.5%)
EEG temporal focus lateralization	Right	32 (32.7%)
	Left	58 (59.2%)

	Not lateralized	8 (8.2%)
MRI	Normal	20 (20.4%)
	Abnormal	23 (23.5%)
	Not available	45 (45.9%)
Antiepileptic drug	Monotherapy	47 (48.0%)
	Polytherapy	51 (52.0%)
Psychotropic drugs	No drugs	78 (79.6%)
	One drug	16 (16.3%)
	Combined therapy	4 (4.1%)

Table 2 – DSM-IV Axis I psychiatric diagnoses.

DIAGNOSIS	N	%
Mood Disorders	42	42.9
Major Depression	24	24.5
Dysthymic Disorder	8	8.1
Past Depressive Episode	6	6.1
Past Manic Episode	2	2.0
Bipolar Disorder	1	1.0
Anxiety Disorders	18	18.4
Generalized Anxiety Disorder	5	5.1
Panic Disorder	4	4.1
Post-Traumatic Stress Disorder	3	3.1
Panic with Agoraphobia	2	2.0
Specific Phobia	2	2.0
Obsessive Compulsive Disorder	2	2.0
Psychotic Disorders	6	6.1

| Substance Abuse | 6 | 6.1 |

Table 3 – Geographical distribution of psychiatric comorbidities in epilepsy.

CONTINENT	COUNTRY	AUTHORS	N	INSTRUMENT	POPULATION	PSYCHIATRIC DISORDERS	MOOD DISORDERS	ANXIETY DISORDERS	PSYCHOSIS	SUBSTANCEE ABUSE
North America	USA	Victoroff, 1994	60	SCID – DSM-III-R	TLE – candidates for surgery	70%	58.3%	31.7%	13.3%	-
		Ettinger et al., 2004	775	CES-D	Epilepsy – community-based	-	36.5%	-	-	-
		Strine et al., 2005	427	Kessler 6 scale	Epilepsy – community-based	-	32.6%	14.4%	-	-
		Kobau et al., 2006	131	Health Style Survey (self-reported depression and anxiety)	Epilepsy – community-based	-	39%	39%	-	-
	Canada	Tellez-Zenteno	253	CIDI	Epilepsy –	23.5%	17.4%	12.8%	-	-

		et al., 2007			community-based					
Europe	UK	Pond and Bidwell, 1960	245	Unstructured psychiatric interview	Children with epilepsy – community-based	29%	-	-	-	-
		Graham and Rutter, 1970	63	Unstructured psychiatric interview	Children with epilepsy – community-based	28.6%	-	-	-	-
		Edeh and Toone, 1987	88	CIS	Epilepsy – selected by general practitioners (GP)	48%	22%	15%	3.4%	-
		Davies et al., 2003	67	SCID	Epilepsy – community-based	37%	-	-	-	-

		Gaitatzis et al., 2004	5834	ICD-9	Epilepsy – selected from a database generated by GP	41%	18.2%	11.1%	9%	2.4%
		Mensah et al., 2006	499	HADS	Epilepsy – from GP	-	11.2%	-	-	-
	Italia	Perini et al., 1996	38	SADS, BDI, STAIX1, STAIX2	JME and TLE (selected) patients	80% (TLE), 22% (JME)	55% (TLE), 17% (JME)	15% (TLE), 11% (JME)	-	-
	Netherlands	Swinkels et al., 2001	209	CIDI	Epilepsy – tertiary epilepsy center	-	24.9%	29.7%	0.5%	20.1%
	Czech Republic	Havlová, 1990	225	Chart review (unstructured)	Cohort of epileptic children	6.7%	-	-	-	-
	Iceland	Gudmundsson,	654	Clinical	Epilepsy	54.5%	-	-	9%	-

		1966		interview (unstructured)	(community-based)					
		Stefansson et al., 1998	241	ICD-9	Epileptic patients receiving benefits	35.3%	-	-	6.2%	5%
	Sweden	Forsgren, 1992	713	Chart review (unstructured)	Epilepsy – community-based	5.9%	-	-	0.7%	-
	Finland	Jalava and Sillanpaa, 1996	94	Chart review and ICD-9	Epilepsy – selected from different sources	24%	-	-	3.1%	-
	Denmark	Bredkjaer et al., 1998	67	ICD-8	Epilepsy – community-based	16.8%	-	-	-	-
Asia	India	Hackett et al., 1998	26	ICD-10	Epilepsy – community-	23.1%	-	-	-	-

					based					
Africa	Nigeria	Gureje et al., 1991	204	CIS	Epilepsy – tertiary center	37%	-	-	30%	-
South America	Brazil	Araújo Filho et al., 2008	270	SCID	Refractory TLE and JME from a tertiary epilepsy center	50% (TLE), 49% (JME)	25.8% (TLE), 19% (JME)	14.1% (TLE), 23% (JME)	15.8% (TLE), 3% (JME)	2% (JME)
		Our study	98	SCID	TLE – selected from a tertiary epilepsy center	54.1%	42.9%	18.4%	6.1%	6.1%

Table 4 – Prevalence of psychiatric comorbidities in our patients and in Porto

Alegre. (Almeida-Filho et al. 1997).

Psychiatric diagnosis	TLE patients (n=98)	General population (n=6471) *
Overall	54.1%	42.5%
Mood disorders	42.9%	11.3%
Anxiety disorders	18.4%	9.6%
Psychotic disorders	6.1%	2.4%
Substance abuse	6.1%	9.2%

Table 5 – Analysis of associations between psychiatric disorders and main clinical aspects of TLE.

	SCID +	SCID -	Risk ($_{95\%}$CI)	*p*
Controlled Epilepsy	20	18		
Uncontrolled Epilepsy	42	18	2.1 (0.9-4.9)	0.09
Unilateral Temporal EEG Spikes	32	19		
Bilateral Temporal EEG Spikes	30	17	1.1 (0.5-2.4)	1.0
Abnormal MRI	12	11		
Normal MRI	12	8	0.6 (0.2-1.6)	0.4
Presence of Aura	43	22		
Absence of Aura	19	14	1.4 (0.6-3.4)	0.5

9.3. ARTIGO nº 3

Tryptophan Hydroxylase 2 gene (*TPH2*) polymorphisms and psychiatric comorbidities in temporal lobe epilepsy

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HIGHLIGHTS

• We studied the influence of TPH2 gene variants on mental disorders in TLE.

• The presence of the A allele in the rs17110747 polymorphism increased the risk of alcohol abuse.

• Serotonergic system has a role in the expression of mental disorders in TLE.

ABSTRACT

Psychiatric comorbidities are frequent in temporal lobe epilepsy (TLE). It is plausible that variance in serotonin-related genes is involved in the susceptibility of these associations. We report here the results on the association of *tryptophan hydroxylase 2* (*TPH2*) gene polymorphisms with psychiatric comorbidities in TLE. A cohort study was conducted on 163 patients with TLE. We assessed the influence of the rs4570625 and rs17110747 polymorphisms in the *TPH2* gene on psychiatric comorbidities in TLE. In patients with TLE, the presence of the T allele in the rs4570625 polymorphism was associated with psychotic disorders (OR=6.28; 95%CI: 1.27 − 17.54; p=0.02), while the presence of the A allele in the rs17110747 polymorphism was associated with alcohol abuse (OR=20.33, 95%CI: 1.60 - 258.46; p=0.02). Moreover, we identified male gender (OR=11.24; 95%CI: 1.68 - 76.92; p=0.01), and family history of psychiatric disorder (OR=15.87; 95%CI: 2.46 − 100; p=0.004) as factors associated with alcohol abuse in TLE as well. Conversely, a family history of epilepsy was inversely associated with alcohol abuse (OR=0.03, 95%CI: 0.001 − 0.60; p=0.02). *Tryptophan hydroxylase 2* gene allele variants might be risk factors for psychiatric conditions in TLE. More specifically, we observed that the T allele in the rs4570625 polymorphism was associated with psychotic disorders, and the A allele in the rs17110747 *TPH2* polymorphism was associated with alcohol abuse in patients with TLE. We believe that this study may open new research venues on the influence of the serotonergic system associated with psychiatric comorbidities in epilepsy.

Keywords: epilepsy, alcohol abuse, serotonergic system, 5-HTT, TPH2.

1. Introduction

Epilepsy is a chronic disorder that affects people of all ages and social levels. It comprises of a group of chronic neurological disorders characterized by recurrent unprovoked seizures, resulting from transitory impairment of brain function due to abnormal neuronal excitability and/or synchronization [1]. Subjects with epilepsy have a greater risk of developing neuropsychiatric comorbidities, especially those with temporal lobe epilepsy (TLE). The main psychiatric disorders involved in TLE are depression, anxiety and psychosis, with prevalences ranging from 11 to 44%, from 15 to 25% and from 2 to 8%, respectively [2-5].

Evidence suggests that the association of psychiatric disorders with epilepsy might be related to common biological substrates [6-8]. A growing body of evidence supports the role of the neurotransmitter serotonin (5-hydroxytryptamine, 5HT) in the regulation, development, propagation and maintenance of seizures [9-12]. In general, preclinical and clinical studies demonstrate an inverse correlation between extracellular brain 5HT levels and susceptibility to seizures, although exceptions have also been described [13]. On the other hand, a large body of evidence shows that low concentrations of serotonin metabolites in plasma and cerebrospinal fluid impair the neuroendocrine responses on stimulation of serotonergic receptors and induce the return of depressive symptoms after successful antidepressant drug treatment, which supports the hypothesis that serotonergic activity is impaired in depression. All effective drugs available for the treatment of depression increase the activity of serotoninergic systems [14-16].

Brain 5HT availability depends on various factors, including the gene encoding the 5HT transporter (5HTT), a cell membrane protein responsible for the clearance of 5HT from the synaptic cleft [17], and monoamine oxidase A (MAO-A), a mitochondrial enzyme responsible for the degradation of 5HT and of other monoamine neurotransmitters [18]. We have previously shown that the C-1019G polymorphism in 5-HT1A was associated with anxiety disorders in patients with TLE [19]. These results opened a precedent to explore the possible role of genetic variants of other serotonergic system-related genes and their involvement on psychiatric comorbidity in patients with epilepsy.

A recently published meta-analysis [20] detected a strong correlation between the rs4570625 polymorphism of the tryptophan hydroxylase-2 (*TPH2*) gene and major depressive disorder. Tryptophan hydroxylase-2 is highly expressed in the raphe nuclei of the midbrain, where it is a rate-limiting enzyme in serotonin synthesis. Tryptophan hydroxylase-2 polymorphisms have been associated with some neuropsychiatric disorders [20-22]. Therefore, it is plausible that polymorphisms of the *TPH2* gene could also modify behavioral traits in patients with epilepsy. In this study, we investigated the association between genetic variants of the *TPH2* gene and psychiatric comorbidity in patients with TLE.

2. Methods

2.1. Patients

A cohort study was conducted on 163 consecutive patients of Western European (white) descent, diagnosed with TLE at the Epilepsy Outpatient Clinic of the Hospital de Clínicas de Porto Alegre (HCPA). Inclusion criteria were based on the 1989 ILAE electroclinical classification [23] and neuroimaging

results. Specifically, we included patients presenting with typical complex focal seizures, with or without generalization, with interictal EEG showing anterior temporal sharp waves, and compatible neuroimaging. Patients with extratemporal epilepsies, mental retardation, and those with systemic diseases were excluded. The study was approved by the Ethics Committee of our institution and is in accordance with the Declaration of Helsinki. All subjects included provided written informed consent to participate in the study.

2.2. Psychiatric interview

All patients were assessed by means of the Structured Clinical Interview for DSM-IV (SCID) [24], divided into six modules, for the detection of one or more lifelong diagnoses of the Axis I Diagnostic and Statistical Manual, fourth edition (DSM-IV) [25]. The Structured Clinical Interview for DSM-IV detected Axis I Psychiatric Diagnoses in 102 (62.6 %) of the 163 patients with TLE (group with TLE with psychiatric comorbidity). In 61 (37.4 %) of the 163 patients with TLE, SCID showed negative results (group with TLE without psychiatric comorbidity). These two groups of patients (group with TLE with psychiatric comorbidity and group with TLE without psychiatric comorbidity) were compared for clinical and genotypic differences.

2.3. Genotyping

Deoxyribonucleic acid was extracted from peripheral blood leukocytes by the salt precipitation method [26]. Subjects were genotyped for the rs4570625 and rs17110747 polymorphisms in the *TPH2* gene [27]. Polymerase Chain Reaction was performed using 20 ng of DNA in SNP Genotyping Assays

provided by Applied Biosystems (Foster City, CA, USA). The procedure that followed the protocol for Taqman SNP Genotyping was also provided by Applied Biosystems, with the use of Taqman Genotyping PCR MasterMix (Applied Biosystems, Foster City, CA, USA). Each assay consisted of unlabeled forward and reverse primers and two reporters that were dye-labeled with FAM and VIC, and were designed for allelic discrimination of specific polymorphisms. Both alleles were scored in a single well by measuring the fluorescence at the end of the PCR reaction.

2.4. Statistical analysis

Categorical variables were compared by using the two-tailed Pearson chi-squared test and Fisher's exact test. Numerical variables were compared by the independent Student t-test, utilizing the Levene test for analysis of equality of variance. All statistical analyses were carried out using the IBM® SPSS® Statistics Package v. 20. Logistic regression was used to examine the independent effect of each variable. To determine the number of independent variables to be included in our logistic regression model, we used the parameters suggested in the literature [28-30]. Results were reported as odds ratio (95% confidence interval) and were considered significant if P was equal to or lower than 0.05.

3. Results

Of the 163 patients with TLE, 57 (35%) were men and 106 (65%) were women. Psychiatric disorders were observed in 102 (62%) of the patients

studied. In our sample, alcohol abuse was observed in 9 (5.5%) patients, 7 (77.8%) of them were male.

The mean ages of patients with epilepsy with psychiatric disorders (group with TLE with psychiatric comorbidity) and those and without psychiatric disorders (group with TLE without psychiatric comorbidity) were 43.4 (SD=12.7) years and 45.3 (SD=12.3) years, respectively, with no significant difference between them (P =0.34). Most (70.6%) of the patients in the group with TLE with psychiatric comorbidity were women, whereas in the group with TLE without psychiatric comorbidity, 55.7% were women and 44.3% were men, a trend towards a significant gender difference (P =0.05). A family history of psychiatric disorders was found in 39.2% of the patients in the group with TLE with psychiatric comorbidity, and in 23% of the patients in the group with TLE without psychiatric comorbidity, a statistically significant difference (P=0.03). The age of onset and duration of disease, the mean seizure frequency, the presence of hippocampal lesion, a left-sided epileptogenic focus, the number of antiepileptic drugs used, a family history of epilepsy, seizure control, interictal EEG activity, the presence of initial precipitating injury and the use of benzodiazepine (BZD) did not differ between patients with TLE with and without psychiatric comorbidities. The clinical and demographic characteristics of patients are presented in Table 1.

The genotype distribution of the rs4570625 and rs17110747 polymorphisms of the *TPH2* gene according to psychiatric disease in patients with TLE is summarized in Table 2. When analyzed together, we found that there was no significant association between these polymorphisms and the presence of neuropsychiatric disorders in patients with TLE, when analyzed

together. However, when each psychiatric disorder was analyzed individually (mood disorder, anxiety disorder, psychosis, and alcohol abuse), the frequency of the rs17110747 polymorphism differed between patients with TLE with and without a history of alcohol abuse, with the frequency of the A allele being lower in patients with a history of alcohol abuse (33.3%) than in individuals without a history of alcohol abuse (22.7%; P=0.049). Moreover, the frequency of the T allele in the rs4570625 polymorphism of the *TPH2* gene was higher in patients with TLE with a history of psychosis (78.6%) than in patients without a history of psychosis (43.6%; P=0.02). No other risk factors in addition to the presence of this allele were associated with psychosis in patients with TLE, even when data were analyzed individually by gender.

Risk factors for alcohol abuse in patients with TLE were the presence of the A allele in the rs17110747 polymorphism of the *TPH2* gene (OR=20.33; 95%CI: 1.60 - 258.46; P=0.02), male gender (OR=11.24, 95%CI: 1.68 - 76.92; P=0.01), and a family history of psychiatric disorders (OR=15.87, 95%CI: 2.46 - 100; P=0.004). It is interesting to note that the presence of a family history of epilepsy was inversely associated with alcohol abuse in patients with TLE (OR=0.03, 95%CI: 0.001 – 0.60; P=0.02). These four factors remained significant after logistic regression. These results are presented in Tables 3 and 4.

4. Discussion

In a previous study, we evaluated the influence of serotonergic-related genes 5-HTTLPR and 5-HTTVNTR polymorphisms on the 5-HTT gene and the C-1019G polymorphism on the 5-HT1A gene in psychiatric comorbidities of

TLE. We observed that the presence of the C allele in the 5-HT1A C-1019G polymorphism was associated with anxiety disorders in TLE. In the same cohort, we now report that the presence of the T allele in the rs4570625 and the A allele in the rs17110747 polymorphisms of the *TPH2* gene was associated with psychosis and alcohol abuse, respectively, in patients with TLE. We were not able to observe any further associations between these polymorphisms and other psychiatric comorbidities. Nevertheless, because they are serotonergic-related genes, our findings point to a possible influence of serotonergic allele variants on psychiatric comorbidities in epilepsy development.

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of serotonin. It converts tryptophan to 5-hydroxytryptophan, which is then decarboxylated to serotonin [31]. Two isoforms, TPH1 and TPH2, are known. While TPH1 is mostly expressed in the periphery and only partially in the brain, TPH2 is exclusively expressed in certain brain neurons [32], particularly in the raphe nuclei, where the vast majority of serotonergic neurons are located [31, 33, 34]. More recently, increasing attention has been given to the role of the *TPH2* gene in mental illnesses, since this is a positional candidate region for various psychiatric disorders, such as major depression and bipolar disorder [20, 21, 35-37]. In this regard, genetic variants of the *TPH2* gene may play an important role in the etiology of psychiatric disorders, as well as their response to treatment, even though there still is no full consensus regarding the specific polymorphisms involved. Thus far to our knowledge, there are no previous studies regarding the involvement of *TPH2* gene polymorphisms in epilepsy or psychiatric comorbidities associated with epileptic disorders. We observed that the presence of the T allele in the rs4570625

polymorphism and of the A allele in the rs17110747 polymorphism of the *TPH2* gene was associated with psychosis and alcohol abuse, respectively, in patients with TLE. Thus, we found evidence that genetic variants of the *TPH2* gene may influence alcohol abuse or psychosis in patients with epilepsy. Further studies are necessary to confirm our findings and elucidate mechanisms involved in these associations.

Serretti and colleagues studied variants in the rs4570625, rs10748185, rs11179027, rs1386498, rs4469933, and rs17110747 polymorphisms of the *TPH2* gene, but were unable to observe any association between these polymorphisms and psychiatric disorders. However, in patients with major depression, some variants in the rs4570625 and rs10748185 polymorphisms were associated with disease severity, although there were no differences in response to drug treatment [21]. Nevertheless, a meta-analysis of 27 studies found an association between rs4570625 polymorphism variants of the *TPH2* gene and major depression [20], thus suggesting that these variants could also be associated with depressive symptoms in epilepsy, a hypothesis that we could not confirm in our cohort of patients with TLE.

Classically, psychotic disorders have been associated with functional changes in dopamine receptors of the striatum and limbic system [38]. However, more recent evidence points to a hypothesis of overlap between phenotypes characterized by schizophrenia-like symptoms more or less prominent in the clinical picture (spectral combinations of symptoms of bipolar disorder and prototypical schizophrenia), as well as overlapping effects of several susceptibility genes influencing these phenotypes [39]. Moreover, the 5-HT1A receptor has attracted particular interest as a potential target for

enhancing cognition in patients with schizophrenia. Along this line, a recent study has shown that chronic treatment with tandospirone, a partial 5-HT1A agonist, leads to recovery of stress-induced lactate production in the prefrontal cortex in a rat model for schizophrenia [40]. This evidence might explain, at least in part, our findings, implying a possible role of serotonin in the development and clinical expression of psychosis in our patients.

Determining the genetic basis of vulnerability to alcoholism is complicated by the fact that any single gene is likely to account for only a small part of the variance. However, there is now growing evidence for the involvement of many types of neurotransmitter receptors and transporters, such as serotonin, dopamine, GABA, opioid, NMDA and nicotinic receptors in the neurobiology of alcohol abuse [41]. We did not find any study provinga functional role for the *TPH2* gene variants evaluated herein, nor do we know to what extent the epileptic disorder of our patients might influence their possible effects. The serotonergic system is important in mediating alcohol reward, preference, dependence, and craving [42]. Deficient 5-HT neurotransmission has been associated with increased alcohol consumption and vulnerability to alcohol dependence [43]. Acute alcohol exposure produces an increase in extracellular 5-HT levels, while chronic exposure causes an overall decrease in 5-HT neurotransmission, as evidenced by lower levels of 5- hydroxyindoleacetic acid (5-HIAA), the primary metabolite of 5-HT, in cerebrospinal fluid of persons with alcohol adiction [44]. This reduction in extracellular 5-HT in a chronic alcohol exposure paradigm could be caused by accelerated 5-HT reuptake from the extracellular space via a serotonin transporter (5-HTT), or by dysfunctional 5-HT release from the raphe nuclei [44]. Nevertheless, it is plausible to

hypothesize that there is a role for genetic variants of the serotonergic system in the biological mechanism leading to alcohol addiction in persons with TLE.

The roles of 5-HT system and genetic variants of serotonin-related genes in the development of psychopathologies are beginning to be elucidated, and it is difficult, with the present knowledge, to explain why a polymorphism in one allelic position might influence alcohol abuse, and why another polymorphism in the same gene might influence psychosis. Future advances focusing on the understanding of a more detailed endophenotypic classification, and, on the other hand, specific epigenetic studies on the complex relationship between several serotonin- and other neurotransmitter-related genes may clarify possible mechanisms involved in these associations.

There are important limitations to our study, which we need to be recognized. The ethnic admixture of the Brazilian sample may be a bias in genetic association studies. However, the population of Rio Grande do Sul State is mainly composed of European descendants (82% of the population) [45], and we included only these patients in our study. Also, the fact that the present sample is in Hardy-Weinberg equilibrium indicates that there may not be important problems of population stratification. In addition to the ethnic stratification limitation discussed above, sample size is an important limitation of this study. Thus, negative results need to be interpreted with caution because of lack of statistical power. Other limitations are the possibility of small allelic effects, allelic heterogeneity, and variation in population substructure. All of these factors have received considerable attention in an attempt to explain the paucity of significant results in psychiatric genetics. Moreover, it is also necessary to consider the possibility of false positive findings due to

confounders, such as different etiology of epilepsies and the presence of hippocampal sclerosis in some patients, but not in others. Finally it would be interesting to evaluate the impact of these genetic variations and respective comorbidities on the quality of life of patients. However, at this time we do not have this information and it might be a theme for further studies that might eventually solve these and other limitations of this study.

5. Conclusions

To our knowledge, the present investigation was the first to study a plausible association between *TPH2* gene polymorphisms and psychiatric comorbidities in epilepsy. We observed that the presence of the T allele in the rs4570625 polymorphism is associated with psychosis, and that the presence of the A allele in the rs17110747 polymorphism is associated with alcohol abuse. Further investigations must be undertaken in order to explore the implications of these associations. In this manner we believe that our study may help to open new possibilities in research regarding the influence of the serotonergic system and other molecular substrates on psychiatric disorders in epilepsy, an area where these studies are still incipient.

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TABLES

Table 1 – Characteristics of patients with TLE with and without psychiatric comorbidities.

Variable	All (*n*=163)	TLE-only (*n*=61)	TLE-psych (*n*=102)	*p*
Mean age (years, SD)	44.1 (12.5)	45.3 (12.3)	43.4 (12.7)	0.34
Mean age of epilepsy onset (years, SD)	19.0 (14.6)	18.6 (14.8)	19.3 (14.5)	0.77
Mean epilepsy duration (years, SD)	25.1 (14.1)	26.7 (13.5)	24.1 (14.5)	0.26
Mean seizure frequency (seizure/month, SD)	2.82 (5.56)	2.02 (4.48)	3.30 (6.09)	0.16
Female sex	106 (65.0)	34 (55.7)	72 (70.6)	0.05*
Initial precipitating injury	41 (25.2)	13 (21.3)	28 (27.5)	0.38
Controlled seizures	63 (38.7)	26 (42.6)	37 (36.3)	0.42
Abnormal MRI	59 (36.2)	26 (42.6)	33 (32.4)	0.39
MTLE-HS or hippocampal atrophy	34 (20.9)	16 (26.2)	18 (17.7)	0.19
Unilateral interictal EEG	91 (55.8)	35 (57.4)	56 (54.9)	0.76
Left-sided focus	121 (74.2)	42 (68.9)	79 (77.5)	0.22
Family history of epilepsy	57 (35.0)	19 (31.1)	38 (37.3)	0.43
Family history of psychiatric disease	54 (33.1)	14 (23.0)	40 (39.2)	0.03*
Monotherapy	83 (50.9)	33 (54.1)	50 (49.0)	0.63
Benzodiazepine use	30 (18.4)	10 (16.4)	20 (19.6)	0.61

Values are presented as frequency (percentage) or mean (SD). TLE-only and TLE-psych groups = patients with temporal lobe epilepsy without and with psychiatric comorbidities, respectively. MTLE-HS is mesial temporal-hippocampal sclerosis. * Significant.

Table 2 – Distribution of TPH2 gene rs4570625 and rs17110747 polymorphisms according to different psychiatric disorders (1), presented by total number of patients and (2) split by sex.

	rs4570625			_p_		rs17110747			_p_
	GG	**GT**	**TT**			**AA**	**AG**	**GG**	
TLE-psych (_n_=102)	53 (52.0)	48 (47.1)	1 (1.0)	0.68		5 (4.9)	19 (18.6)	78 (76.5)	0.88
Male-psychiatric	15 (14.7)	15 (14.7)	0 (0.0)	0.60		3 (2.9)	3 (2.9)	24 (23.5)	0.33
Female-psychiatric	38 (37.3)	33 (32.4)	1 (1.0)	0.68		2 (2.0)	16 (15.7)	54 (52.9)	0.86
Psychosis (_n_=14)	3 (21.4)	11 (78.6)	0 (0.0)	**0.02***		1 (7.1)	1 (7.1)	12 (85.7)	0.45
Male-psychosis	0 (0.0)	3 (21.4)	0 (0.0)	0.09		1 (7.1)	0 (0.0)	2 (14.3)	0.26
Female-psychosis	3 (21.4)	8 (57.1)	0 (0.0)	0.16		0 (0.0)	1 (7.1)	10 (71.4)	0.37
Alcohol abuse (_n_=9)	4 (44.4)	5 (55.6)	0 (0.0)	0.82		2 (22.2)	1 (11.1)	6 (66.7)	**0.049***
Male-alcohol	3 (33.3)	4 (44.4)	0 (0.0)	0.69		2 (22.2)	0 (0.0)	5 (55.6)	0.06
Female-alcohol	1 (11.1)	1 (11.1)	0 (0.0)	0.98		0 (0.0)	1 (11.1)	1 (11.1)	0.63
Anxiety disorder (_n_=52)	26 (50.0)	25 (48.1)	1 (1.9)	0.31		3 (5.8)	11 (21.2)	38 (73.1)	0.71
Male-anxiety	5 (9.6)	7 (13.5)	0 (0.0)	0.35		1 (1.9)	3 (5.8)	8 (15.4)	0.59
Female-anxiety	21 (40.4)	18 (34.6)	1 (1.9)	0.43		2 (3.9)	8 (15.4)	30 (57.7)	0.58
Mood disorder (_n_=73)	37 (50.7)	35 (48.0)	1 (1.4)	0.47		4 (5.5)	13 (17.8)	56 (76.7)	0.77
Male-mood	11 (15.1)	7 (9.6)	0 (0.0)	0.57		3 (4.1)	1 (1.4)	14 (19.2)	0.07
Female-mood	26 (35.6)	28 (38.4)	1 (1.4)	0.34		1 (1.4)	12 (16.4)	42 (57.5)	0.79

Values are presented as frequency (percentage). TLE-only and TLE-psych groups = patients with temporal lobe epilepsy without and with psychiatric comorbidity. * Significant.

Table 3 – Clinical and demographic characteristics of patients with TLE with psychosis and alcohol abuse.

Variable	All patients (*n*=163)	No psychosis (*n*=149)	Psychosis (*n*=14)	*p*	No alcohol abuse (*n*=154)	Alcohol abuse (*n*=9)	*p*
Mean age (years, SD)	44.1 (12.5)	44.2 (12.3)	43.7 (15.2)	0.90	44.2 (12.7)	42.9 (10.2)	0.76
Mean age of epilepsy onset (years, SD)	19.0 (14.6)	19.3 (14.8)	16.6 (11.7)	0.51	18.8 (14.5)	22.7 (15.5)	0.44
Mean epilepsy duration (years, SD)	25.1 (14.1)	24.9 (14.3)	26.4 (12.4)	0.68	25.4 (14.3)	20.2 (9.9)	0.29
Male sex	57 (35.0)	54 (36.2)	3 (21.4)	0.38	50 (32.5)	7 (77.8)	**0.01***
Family history of epilepsy	57 (35.0)	50 (33.6)	7 (50)	0.22	56 (36.4)	1 (11.1)	0.16
Family history of psychiatric disease	54 (33.1)	50 (33.6)	4 (28.6)	1.00	47 (30.5)	7 (77.8)	**0.01***
Controlled seizures	76 (46.6)	69 (46.3)	7 (50)	0.79	72 (46.8)	4 (44.4)	1.00
Lateralized interictal EEG	150 (92.0)	136 (91.3)	14 (100)	0.51	143 (92.9)	7 (77.8)	0.26
Initial precipitating injury	41 (25.2)	38 (25.5)	3 (21.4)	1.00	37 (24.0)	4 (44.4)	0.23
Benzodiazepine use	30 (18.4)	25 (16.8)	5 (35.7)	0.14	27 (17.5)	3 (33.3)	0.37
rs4570625 T allele	76 (46.6)	65 (43.6)	11 (78.6)	**0.02***	71 (46.1)	5 (55.6)	0.82
rs17110747 A allele	38 (23.3)	36 (24.2)	2 (14.3)	0.45	35 (22.7)	3(33.3)	**0.02***

Values are presented as frequency (percentage) or mean (SD). * Significant.

Table 4 – Logistic regression results showing risk factors for alcohol abuse in TLE.

Variable	No alcohol abuse	Alcohol abuse	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p
rs17110747 A allele	35 (22.7)	3 (33.3)	8.55 (1.40–52.63)	20.33 (1.60-258.46)	**0.02***
Male sex	50 (32.5)	7 (77.8)	7.28 (1.46–36.30)	11.24 (1.68–76.92)	**0.01***
Family history of epilepsy	56 (36.4)	1 (11.1)	0.22 (0.03–1.80)	0.03 (0.001-0.60)	**0.02***
Family history of psychiatric disorder	47 (30.5)	7 (77.8)	7.97 (1.60–39.80)	15.87 (2.46-100.00)	**0.004***

Values are presented as frequency (percentage) or means (SD).* Significant.

9.4.   ARTIGO nº 4

Is interictal EEG activity a biomarker for mood disorders in temporal lobe epilepsy?

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HIGHLIGHTS:

- We quantified EEG interictal spikes in a cohort of patients with temporal lobe epilepsy, with or without psychiatric comorbidities.

- Patients with a lifetime history of mood disorders showed a lower EEG interictal spike index (<60/h) than patients with no psychiatric diagnosis.

- EEG interictal spikes might be an interesting neurophysiological biomarker for mood disorders in temporal lobe epilepsy.

ABSTRACT:

Objective: Psychiatric comorbidities are frequent in temporal lobe epilepsy (TLE), and symptoms of these comorbidities may be related to epilepsy activity. Here we evaluated interictal EEG activity in TLE patients with or without psychiatric comorbidities.

Methods: Cohort study of 78 patients with TLE, with evaluation of wake/sleep interictal scalp EEG. All subjects were submitted to psychiatric structured clinical interview (SCID) for the diagnosis of lifetime psychiatric comorbidities. Three major diagnostic categories were studied: mood disorders, anxiety disorders, psychosis. We then evaluated differences in interictal EEG activity between patients with and without these psychiatric comorbidities.

Results: Infrequent EEG interictal spikes, defined as less than one event per minute, were significantly associated with mood disorders in TLE ($p = 0.02$).

Conclusions: Mood disorders in patients with TLE might be associated with low interictal spike frequency on EEG. Low intensity seizure disorder has been associated with a decrease in interictal EEG discharges and with an increase in psychiatric symptoms in TLE, a phenomenon known as forced normalization. In the present study, we perhaps observed a neurophysiological correlate in line with forced normalization.

Significance: A low spike index in TLE might be an interesting neurophysiological substrate associated with the complex relationship between epilepsy and depression, as expressed by the phenomena of forced normalization and bidirectionality between these two entities.

1. **Introduction**

Temporal lobe epilepsy (TLE) is the most frequent form of partial epilepsy in adults (Hauser et al., 1996; Picot et al., 2008). From a topographic point of view, this type of epilepsy is divided into mesial temporal lobe epilepsy (MTLE) and neocortical temporal lobe epilepsy (NTLE), according to the networks and structures affected by the seizure disorder (Kahane and Bartolomei, 2010; Tatum, 2012; Kennedy and Schuele, 2012). Although some semiologic characteristics are more or less specific for each subtype of TLE, a distinct electroclinical differentiation between the two conditions is not always possible. While MTLE the syndrome due to hippocampal sclerosis has stereotyped manifestations, the clinical, electrophysiological, and neuroradiological manifestations of NTLE are more heterogenous (Phänder et al., 2002; Maillard et al., 2004). TLE is commonly refractory to pharmacological treatment, frequently requiring surgical resection (Wiebe et al., 2001; Wieser, 2004; Thom et al., 2010). Moreover, TLE is frequently associated with mental disorders, especially depression and anxiety (Bragatti et al., 2010a; Dalmagro et al., 2012; Rudzinski and Meador, 2013).

The EEG is a valuable tool for the diagnosis of epilepsy (Noachtar and Rémi, 2009). In patients suspected of having epilepsy, the interictal EEG often demonstrates epileptiform activity and other nonspecific abnormalities (Kennett, 2012). Interictal epileptiform activity includes spikes, sharp waves, and paroxysmal fast activity, and their combinations with slow waves (de Curtis et al., 2012). They represent brief paroxysmal discharges that arise from synchronous neuronal firing. They are associated with changes in cerebral blood flow and cerebral metabolism, and can affect cognition as well (Rodin et

al., 2009). EEG showing interictal epileptiform activity indicates an increased risk of having seizures, and may support a diagnosis of epilepsy when the clinical information is not definitive (Rodin et al., 2009). The distribution and topographic localization of spike activity aid in the classification of the epilepsy syndrome.

The temporal lobe is the most epileptogenic region of the human brain. MTLE is a group of disorders that predominantly involves dysregulation of hippocampal function caused by neuronal hyperexcitability (Schwartzkroin, 1986). In TLE, and particularly in MTLE, spikes are highly restricted to anterior temporal electrodes (Williamson et al., 1993; Hamer et al., 1999; Noachtar and Rémi, 2009; Dworetzky and Reinsberger, 2011). Interictal scalp EEG provides reliable lateralizing information (Sammaritano et al., 1987; So, 2001) and is of prognostic postoperative value in patients submitted to surgical treatment (Aronica et al., 2001; Hildebrandt et al., 2005).

Depression is the most common psychiatric comorbidity in epilepsy (Christensen et al., 2007; Tellez-Zenteno et al., 2007; Bragatti et al., 2010a; 2011; Dalmagro et al., 2012). Through various cross-sectional population studies, it has been estimated that the prevalence of lifetime depressive symptoms in patients with epilepsy is around 4.1-32.5% (Kanner, 2008a; Fiest et al., 2013). Several psychological, physiological and neurobiological factors contribute to this comorbidity (Kanner, 2008b). Subjects with epilepsy and depressive symptoms have a poorer quality of life (Gilliam et al., 1997, Boylan et al., 2004), are more likely to experience side effects of antiepileptic drugs (Kanner, 2007), are more often drug-refractory (Hitiris et al., 2007), and have a

poorer outcome after epilepsy surgery (Kanner, 2008a; 2013; Busch et al., 2011; de Araújo Filho, 2012; Cleary et al., 2013).

Patients with TLE are more likely to have depressive symptoms than other groups (Robertson, 1985; Quiske et al., 2000; Dalmagro et al., 2012; Kanner et al., 2012). On the other hand, a number of studies have also suggested an association between hippocampal volume loss and mood disorders (Bremner et al., 2000; Frodl et al., 2002; Du et al, 2012; Suzuki et al, 2013), revealing a plausible underlying involvement of the limbic system in the depressive symptoms of patients without neurological disorders, as also observed in patients with TLE.

As far as we know, there are few studies assessing the influence of psychiatric comorbidities on interictal EEG activity in patients with TLE (Baskaran et al., 2012), and also few quantitative EEG studies which have found associations between biomarkers derived from the analysis of the EEG background activity (change in the activity of EEG frequency bands, hemispheric alpha asymmetry, theta cordance, the antidepressant treatment response index) and the degree of response to antidepressant medication in patients with major depression.

In the present study we evaluated the interictal EEG characteristics, especially the frequency of epileptic discharges, in a cohort of patients with TLE, in order to determine a possible association between these characteristics and the presence or absence of psychiatric comorbidities. In our view, studying interictal epileptiform activity might help to the advance in the knowledge about the epileptic disorder as a whole, going beyond the mere understanding of epileptic seizures.

1. Methods

2.1. Patients

The study was conducted on a cohort of 78 consecutive patients with a diagnosis of TLE (53 women, 25 men), from the Adult Epilepsy Outpatient Clinic at Hospital de Clinicas de Porto Alegre. Inclusion criteria were the presence of electroclinical and neuroimaging features of TLE according to the ILAE Classification for Epileptic Seizures and Syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Patients less than 18 years old or with generalized epilepsies, extratemporal epilepsies, mental retardation (IQ scores below 70), brain tumors, systemic diseases, or penetrating head trauma were excluded.

Neuroimaging (CT scan and MRI) was positive in 34 patients (43.6%) whose main structural lesions were: hippocampal sclerosis (19 patients, 55.9%), and hippocampal atrophy (5 patients, 14.7%). A cystic lesion involving the temporal lobe was observed in 2 patients. We found a variety of temporal lesions in only 1 patient each: focal cortical dysplasia, isolated calcification, low-grade glioma, and meningioma.

2.2. EEG recording and evaluation

As recommended by international guidelines (American Clinical Neurophysiology Society, 2006), all patients had at least one scalp EEG recording. We used the 10-20 International System for electrode placement, with impedance maintained below 5kΩ. Tracings were analyzed with a

referential montage using a common average reference. Low and high frequency filters were set at 0.3 Hz and 70 Hz, respectively, with a notch filter of 60 Hz. The mean duration of the recordings was 38 minutes, with awake patients being activated by a 3-minute hyperventilation and photic stimulation. A phase II-sleep recording was always achieved.

Tracings were blindly analyzed by two experienced and certified electroencephalographers (J.A.B. and C.M.T.), who evaluated the following quantitative aspects: total duration of recording, total number of discharges, mean spike frequency, and left-right proportion of discharges. We considered unilateral every predominance of one hemisphere over the other if >90%. After categorization, mean spike frequency (<1 spike/minute and >1 spike/minute) and extension of irritative activity (unilateral versus bilateral/generalized) were also analyzed. A counting of spikes was performed visually using the criteria for definition of epileptiform discharges established by the IFCN glossary (Noachtar et al., 1999).

2.3. Psychiatric interview

After giving written informed consent, all patients answered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001), which is divided into six modules for the detection of one or more lifetime diagnoses using the Axis I Diagnostic and Statistical Manual, fourth edition (DSM-IV) (American Psychiatric Association, 2000). Questionnaires were applied by researchers who were blind to epilepsy diagnosis of the patient. Patients with a psychiatric diagnosis were subdivided into 3 groups: mood disorders, anxiety disorders, psychosis. Twenty-four patients had a mood-anxiety disorder

association. Psychosis and anxiety were associated in four patients, psychosis and mood disorders in three.

2.4.   Statistical analysis

Categorical variables were compared by the two-tailed Pearson Chi-Square test, and Fisher exact test. Numerical variables were compared by the independent Student t-test, with the Levene test for analysis of equality of variance. All statistical analyses were carried out using the IBM® SPSS® Statistics 20. In order to examine the independent effect of each variable we used Backward Stepwise (Wald) logistic regression. Because we observed an association between depression and female gender and anxiety symptoms in a previous study, we forced the entry of these variables into the regression model (Schenkel et al., 2012). To determine the number of independent variables to be included in our logistic regression model we used the parameters suggested in the literature (Tabachnick and Fidell, 1996). Positive neuroimaging findings were also included in the model, because it is biologically plausible to assume that they might be another independent predictive factor for mood disorders. Results are reported as odds ratio (95% confidence interval), as a measure of association between exposure (spike rate index) and outcome (psychiatric disorder), and were considered significant if p was equal or less than 0.05.

2.   Results

Of the 78 patients, 53 (68%) were women and 25 (32%) were men. Psychiatric disorders were observed in 50 (64%) of the patients studied. In our sample, 38 individuals had mood disorders (48.7%), 28 of them being females

(73.7%). Anxiety disorders were present in 24 patients (30.8%), 16 of them females (66.7%). Ten patients had psychosis (12.8%), 8 of them females (80%).

The mean age of epileptic patients with psychiatric disorders (TLE-psych group) and without psychiatric disorders (TLE-only group) were 41.7 (SD=1.8) and 45.1 (SD=11.4) years, respectively, with no significant difference between them (p =0.24). In this group of patients, there was no difference between TLE-psych and TLE-only groups in terms of gender, with about 68% of women, and 32% of men in both groups (p =0.99). A family history of psychiatric disorders was observed in 40% of the TLE-psych group, and in 21.4% of TLE-only group, but this difference was not statistically significant (p=0.14). The age at onset and duration of disease, family history of epilepsy, seizure control, interictal EEG activity, presence of initial precipitating injury, and use of benzodiazepine (BZD) did not differ between TLE patients with and without psychiatric comorbidities. The clinical and demographic characteristics of the sample are presented in Table 1.

Table 2 shows EEG data obtained for the groups with and without psychiatric comorbidities. There were no differences in terms of duration of EEG recording, total number of spikes counted, and frequency of patients with unilateral discharges in any of the psychiatric disorders studied. However, the number of patients with TLE and a spike index lower than 1/minute was statistically significant when we compared patients with and without mood disorder. Twenty-five patients (65.8%) with mood disorders had less than 60 spikes/hour in their EEG, while only 16 (40%) of the patients without mood disorder had less than 60 spikes/hour. We also found a similar statistically

significant result for alcohol abusers, but the sample size was too small to make a definitive statement. See Table 3.

Together with spike index, gender, associated anxiety disorder, and positive neuroimaging findings were forced into a Backward Stepwise logistic regression (Wald) model. However, only spike index remained as an independent risk factor for mood disorder in TLE (patients with less than 1 spike/minute had an Adjusted Odds Ratio=2.89, (95% CI): 1.15 – 7.25; p=0.02; see Table 4). Thus, in our study, the frequency of epileptiform discharges was independently and inversely associated with a diagnosis of mood disorder.

3. Discussion

3.1. TLE and mood disorder relationships

TLE is associated with depressive symptoms due to several mechanisms. One plausible explanation is the stigma affecting the daily life of individuals with epilepsy, and which clearly exerts a negative influence on the quality of life of these patients, predisposing them to depressive symptoms (Grant et al., 2013). Moreover, evidence from animal models and human studies suggests common underlying pathogenic mechanisms that also may explain the comorbidity of depression and epilepsy. For example, decreased concentrations of serotonin in the synaptic cleft play an epileptogenic role in both animal and human studies of epilepsy, and are also associated with major depression (Bhagwagar et al., 2002; Booij et al., 2002; Kanner, 2013). Positron emission tomography studies in major depression and epilepsy suggest dysfunction of serotonergic receptors (Theodore et al., 2006; Theodore et al., 2012). GABAergic potentiation may also precipitate depression in patients with

a genetic predisposition to mood disorders, as is the case for the use of

GABAergic antiepileptic drugs (eg.: barbiturates and valproate) (Mula et al.,

2007; Kanner, 2013).

In turn, depression is also associated with an increased risk to

develop epilepsy (Hesdorffer et al., 2006). This bidirectionality reinforces the

general hypothesis that both disorders share common neurobiological

mechanisms underlying the clinical symptoms presented by the patients

(Catena-Dell'Osso et al., 2013). These mechanisms include hyperactivity of the

hypothalamic-pituitary-adrenal axis, structural and functional abnormalities of

cortical structures, increased glutamatergic and decreased GABAergic and

serotonergic activity, and immunological abnormalities (Kanner, 2012; Valente

and Busatto Filho, 2013).

Alterations and neurotransmission disturbance among critical

anatomical networks, and impaired or aberrant plastic changes might

predispose TLE patients to neuropsychiatric and mood disorders (Bragatti et al,

2010b; Schenkel et al., 2010; 2012; Bianchin et al., 2011; Kandratavicius et al.,

2012). Studies in animal models point to some potential mechanisms that could

explain epilepsy and depression comorbidity, such as various components of

the dopaminergic, noradrenergic, serotonergic, and GABAergic systems, as

well as key brain regions like the amygdala and hippocampus (Epps and

Weinshenker, 2013). Although complex, there is a close correlation between

epilepsy, especially TLE, and mood disorders. Our hypothesis is that a

dysfunction of the same neural circuitry occurs in both conditions, with different

intensities.

3.2. Antidepressant drugs and seizure threshold

Another important issue to be discussed is the impact of antidepressant medicines on the generation of epileptic seizures. Although the treatment with antidepressant drugs of patients with epilepsy and depressive disorders is considered safe, some of these agents can potentially cause or exacerbate epileptic seizures. This is particularly true for tricyclic antidepressants (Kanner, 2013). This decrease in the seizure threshold was documented in animal models of epilepsy, and might involve, among others, the serotonergic system (Epps and Weinshenker, 2013). Patients with a history of seizures may show increased numbers of epileptiform discharges following administration of intravenous imipramine (Kiloh et al., 1961) and amitriptyline (Davison, 1965). Moreover, high doses of several types of medications may elicit spikes or polyspikes that usually appear bisynchronously in bursts, either spontaneously or as a photoparoxysmal response (Bauer and Bauer, 2005; Blume, 2006). Our study was not designed to assess a causal relation between antidepressant drugs and an increase in the frequency of interictal spike. However, it is interesting to observe that 12 (15.4%) of our patients were using an antidepressant agent, mostly a tricyclic drug, but only four of them (33.3%) had a mean spike frequency > 1minute. Thus, there must be other explanations for our finding of a lower rate of EEG interictal discharges in depressed patients than an effect of antidepressant drugs. Anyway, these data reinforce the hypothesis that depressive symptoms and epileptiform activity ocupy opposite places.

3.3. Forced normalization

The concept of Forced Normalization dates back to the publications of Heinrich Landolt (1958). Originally, Landolt described a group of patients with epilepsy who had psychotic events associated with the disappearance of the epileptiform discharges on the EEG, and coined the term "forced normalization" to depict the improvement or normalization of the EEG during the time the patient was psychotic. Interestingly, the introduction of a particular drug (etosuximide) led to an increase in the number of cases (Trimble and Schmitz, 1998). In 1951, Gibbs (1951) had already reported intensification of psychiatric disorders in temporal lobe seizures when seizures were suppressed.

Along this line, GABAergic drugs such as vigabatrin sometimes produce depressive symptoms linked tothe control of seizures, a form of forced normalization (Mula and Monaco, 2009). This in turn could explain our results showing an, association of a less severe form of epileptiform EEG pattern (<1 spike/minute) with mood disorders.

4.4. Significance of epileptiform discharges

In neurologic practice, interictal spikes on the EEG recording are used to confirm a diagnosis of epilepsy and to help identify a patient's epilepsy syndrome. Spikes are a biomarker for the underlying pathophysiology of the epileptic condition. Patients with TLE with rare spikes might have a less severe form of epilepsy than those with a greater spiking rate (Rosati et al., 2003).

Another study (Janszky et al., 2005) showed that seizure frequency and epilepsy duration were independently associated with the frequency of interictal epileptiform discharges (IED), suggesting that IED are modulated by seizures. In our study we found an association between low frequency of interictal discharges and a diagnosis of mood disorder, but we did not observe an association between spike frequency and control of seizures or epilepsy duration.

In a study with SPECT of 16 patients with polymicrogyric cortex, Wichert-Ana et al. (2008) observed that patients with interictal hyperperfusion within the polymicrogyric cortex had a significantly higher spike rate on the interictal EEG than patients with normal perfusion. In depression, there must be a less severe form of cortical hyperexcitability, partially explaining the lower interictal spike frequency observed in our study (Kondziella et al., 2007; Kanner, 2012). Recent evidence supporting the existence of a pre-ictal state distinguishable from the interictal state, with a different physiological basis responsible for each state (Stafstrom, 2011), suggests a future target for the prevention of recurrent seizures.

4.5. Limitations and strengths of the study

We recognize that our study has many limitations. First of all, our sample is relatively small, and this imposes an additional difficulty regarding extrapolation of the results. The parameters used to record the EEG traces were not fully standardized (duration, sleep depth achieved), but when the results were analyzed statistically, there were no significant differences between

the exams performed. Another important limitation when we try to study mood disorders in individuals with epilepsy is the fact that SCID does not detect an important interictal condition related to a dysfunction in the affect, i.e, interictal dysphoria. Up to 70% of patients who were consecutively assessed for the occurrence of depression could be classified as having atypical features, especially in the presence of drug-resistant epilepsy (Kanner et al., 2004). The term interictal dysphoric disorder was coined by Blumer (2000) to refer to a type of somatoform-depressive disorder seen in these patients which might be linked to TLE (Mula et al., 2010). If we could have made this diagnosis in our patients, we could probably have found more consistent data.

However, our study has some strengths that need to be emphasized as well. Patients were evaluated with SCID and psychiatric diagnosis was blind to epilepsy characteristics. Moreover, EEGs were evaluated by experienced electrophysiologists who were blind to the psychiatric diagnosis. Finally, our findings are biologically plausible since there is extensive literature suggesting that antidepressants increase interictal epileptiform activity, and that improvement in this EEG parameter has been associated with worsening of psychiatric symptoms, both findings in line with our observation.

4. Conclusions

Our data suggest an inverse relation between frequency of interictal spikes on EEG and a diagnosis of mood disorder in TLE. Taking into account evidence establishing common biological mechanisms linking both conditions, particularly with the involvement of the limbic system, it is plausible to assume

that interictal EEG spike index in patients with TLE could be a biomarker for

prediction of the development of depressive symptoms in these patients,

representing a neurophysiological substrate for the clinical manifestations of a

common dysfunction of a specific neuronal circuitry (perhaps in different

extension and intensity). In our study, we observed an interesting inverse

association between interictal EEG activity and depressive symptoms.

Nevertheless, further studies in the area would shed more light on this

fascinating issue.

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Fig. 1 – interictal EEG of a 44 y.o. male patient with a diagnosis of Major Depression. Tracing showed infrequent focal spikes involving left anterior temporal region.
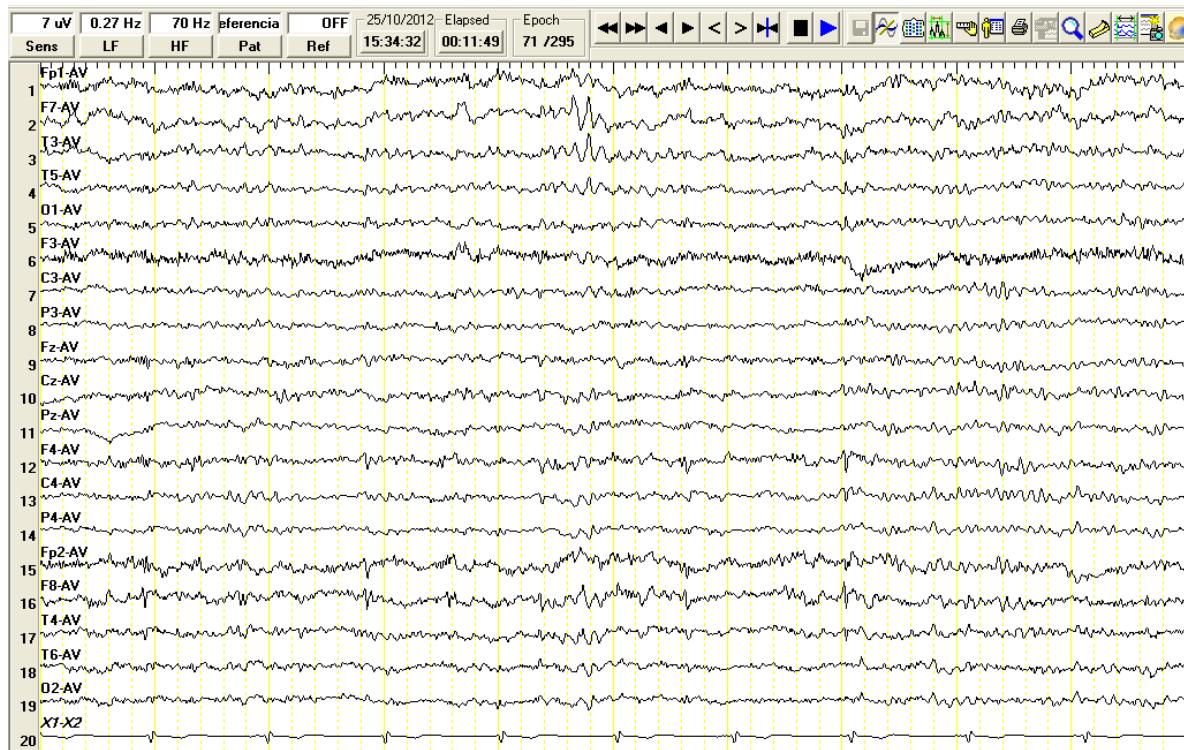
Fig. 2 – interictal EEG of a 26 y.o. female patient without any psychiatric diagnosis. Frequent focal spikes involving right anterior temporal region are seen (20s/page).

Table 1 – Characteristics of our TLE patients with and without psychiatric comorbidities.

Variable	All (*n*=78)	TLE-only (*n*=28)	TLE-psych (*n*=50)	*p*
Mean age (years, SD)	42.9 (11.7)	45.1 (11.4)	41.7 (11.8)	0.24
Mean age at epilepsy onset (years, SD)	18.8 (13.5)	19.8 (12.9)	18.2 (13.9)	0.28
Mean epilepsy duration (years, SD)	24.0 (13.2)	25.3 (13.4)	23.2 (13.1)	0.45
Female sex	53 (68.0)	19 (68.0)	34 (68.0)	0.99
Family history of epilepsy	25 (32.1)	7 (25.0)	18 (36.0)	0.38
Family history of psychiatric disease	26 (33.3)	6 (21.4)	20 (40.0)	0.14
Controlled seizures	37 (47.4)	14 (50.0)	23 (46.0)	0.73
Unilateral interictal EEG	43 (55.1)	15 (53.6)	28 (56.0)	0.06
Positive neuroimaging findings	34 (43.6)	15 (53.6)	19 (38.0)	0.06
Initial precipitating injury	17 (21.8)	7 (25.0)	10 (20.0)	0.78
Benzodiazepine use	11 (14.1)	4 (14.3)	7 (14.0)	1.00

Values are presented as frequency (percentage) or mean (SD). TLE-only and TLE-psych groups = temporal lobe epilepsy patients without and with psychiatric comorbidities, respectively.

Table 2 – Interictal EEG characteristics according to the presence of psychiatric disorders.

Variable	TLE-psych (*n*=50)	TLE-only (*n*=28)	*p*
Duration of recording (SD)	37.9 (11.5)	38.7 (18.7)	0.50
Total spikes counted (SD)	57.1 (78.2)	91.3 (111.1)	0.67
Mean spikes/minute (SD)	1.6 (2.4)	2.6 (3.2)	0.12
Unilateral discharges (%)	11 (22)	5 (17.9)	0.66

Values are presented as frequency (percentage), except for duration of recording, which is shown in minutes.
TLE-only and TLE-psych groups = temporal lobe epilepsy patients without and with psychiatric comorbidities, respectively.

* Significant.

Table 3 – Interictal EEG characteristics in the different psychiatric disorders.

Variable	Duration of recording (SD)	Total spikes counted (SD)	Mean spikes/min <1 (%)	Unilateral discharges (%)
Mood disorder (*n*=38)	37.9 (12.0)	49.1 (71.1)	25 (65.8)	35 (92.1)
No mood disorder (*n*=40)	38.4 (6.5)	88.7 (105.8)	16 (40.0)	36 (90.0)
***P* for mood disorder**	0.72	0.58	**0.02***	0.49
Anxiety disorder (*n*=24)	38.5 (10.4)	52.8 (74.5)	15 (62.5)	21 (87.5)
No anxiety (*n*=54)	38.0 (15.9)	76.8 (98.8)	26 (48.2)	50 (92.6)
***P* for anxiety disorder**	0.49	0.76	0.24	0.19
Psychosis (*n*=10)	40.3 (8.0)	71.7 (90.8)	5 (50.0)	9 (90.0)
No psychosis (*n*=68)	37.8 (15.1)	69 (93.0)	36 (52.9)	62 (91.2)
***P* for psychosis**	0.38	0.21	0.86	0.91

Values are presented as frequency (percentage) or mean (SD). *Significant.

Table 4 – Risk factors for mood disorders in TLE after logistic regression.

Variable	Mood disorder (n=38)	No mood disorder (n=40)	Crude OR (95%CI)	Adjusted OR (95% CI)	Adjusted p
Infrequent Spikes (<1/min)	25 (65.8)	16 (40.0)	2.86 (1.15 – 7.14)	2.89 (1.15-7.25)	**0.02***
Female Sex	28 (73.7)	25 (62.5)	1.67 (0.64 – 4.35)	1.91 (0.68-5.32)	0.29
Anxiety Disorder	15 (39.5)	9 (22.5)	2.25 (0.84 – 6.03)	2.04 (0.74 – 5.56)	0.10
Positive Neuroimaging	9 (23.7)	14 (35.0)	1.74 (0.64 – 4.67)	1.47 (0.51 – 4.35)	0.33

Values are presented as frequency (percentage) or means (SD). OR=odds ratio.* Significant.

10.   ANEXOS: OUTRAS PUBLICAÇÕES NO PERÍODO

10.1.   Clin Neurophysiol 2011; 122: 1069-70.

Editorial

Recognition of seizures in neonatal intensive care units

The neonatal period, i.e., the first four weeks of life, is the time when the brain has the lowest seizure threshold. Seizures occur in 1.8 to 5/1000 live births in the United States (Jensen, 2009), and are caused by hypoxic, ischemic, hemorrhagic, infectious or metabolic derangements of the brain, or may occur spontaneously. By far, the most common cause of symptomatic neonatal seizures is hypoxic-ischemic encephalopathy, which represents two thirds of all neonatal seizures (Tekgul et al., 2006). Importantly, clinical neonatal seizures in the setting of birth asphyxia are associated with worse neurodevelopmental outcome, which includes the late development of epilepsy, regardless of the severity of the insult to the brain (Glass et al., 2009). Thus, recognition and treatment of clinical and subclinical seizures in at-risk neonates are theoretically central for a significant reduction in morbidity and mortality associated with neonatal encephalopathy (Mc Bride et al., 2000).

Since 80% of electrographic neonatal seizures are not accompanied by clinical manifestations (*subclinical seizures*), EEG is essential for diagnosis (Clancy, 2006). Indeed, conventional EEG (cEEG) is still considered the gold standard for neonatal seizure recognition in the neonatal intensive care units

(NICU). Unfortunately, this approach is not always feasible in the NICU, first because it requires the application and maintenance of too many electrodes, second because it demands qualified EEG technologists, and finally because it usually depends on the availability of a 24-hour clinical neurophysiologist.

Amplitude-integrated EEG (aEEG) is a method of simplified EEG monitoring, and represents a useful tool for continuous assessment of electrical brain function in the NICU (Rosén, 2006). This method is based on a time-compressed (usually 6 cm/h) semilogarithmic display of peak-to-peak amplitude of the EEG signal values, asymmetrically filtered (bandpass of 2 to 15 Hz), to extract the activity centered in the alpha band. The rational for this processing is to minimize low- and high-frequency artifacts (Toet et al., 2008). The aEEG has found an increasing clinical application in the NICU, and is particularly useful for the assessment of background pattern; presence, quality and time of onset of sleep-wake cycling; and detection of epileptic seizure activity in neonates (De Vries and Toet, 2006, Toet and Lemmers, 2009).

Recently, several papers have been published measuring the accuracy of aEEG for detecting epileptic seizure activity (Bourez-Swartz et al., 2009; Shah et al., 2008; Shellhaas and Clancy, 2007). In general, sensitivity varied between 76% and 92%, which in turn makes aEEG a reliable tool for long-term monitoring of at-risk neonates. Variation in the results are probably related to distinct seizure characteristics (rate, duration, localization), technical issues (number of electrodes used), and expertise of interpreters. Regarding seizure characteristics, in the study of Shelhaas and Clancy (2007), using aEEG, less than a half of neonatal seizures in the frontal regions could be detected; the same low sensitivity was found for longstanding episodes (i.e., status

epilepticus). Considering the number of electrodes, van Rooij et al. demonstrated that placement of additional electrodes could provide significant additional information, particularly a few concerning the background pattern in babies with unilateral injuries (van Rooij et al., 2010a). Moreover, Bourez-Swartz et al. found a slightly better seizure pattern detection rate with multichannel aEEG, compared with single channel (C4-C3) aEEG (Bourez-Swartz et al., 2009).

The study by Frenkel et al., in this issue (Frenkel et al., 2010), focuses on the interpreter's skill in the use of aEEG for detection of neonatal seizures. They compared cEEG with aEEG, using readers with different levels of expertise. For aEEG, readers were a neonatologist, a fellow and a medical student. On the other hand, cEEG was assessed by two neurologists and a neonatologist (blind for previous aEEG). The other main objective of the study was to assess the ability of aEEG to detect seizures before cEEG recordings are obtained. Each 10 minute epoch of aEEG recording was time-locked to a concordant cEEG epoch. Next, each epoch was blindly assessed for seizure activity by three independent investigators for each modality. Seizure activity was defined as an abrupt rise of the lower border with a simultaneous rise of the upper border of the recorded strip, with a simultaneous raw EEG seizure activity of at least 10 seconds duration (Hellstrom-Westas and Rosen, 2006). Concordance between methods and readers was analyzed by epochs and by seizure episodes detections separately.

When compared with cEEG, specificity of the student's aEEG assessment was low, especially per seizure episode detection. In contrast, good agreement was found between the results of both the fellow and the

neonatologist. Accuracy of non-expert use of aEEG, with concomitant inter-observer agreement for seizure detection using this method (called cerebral function monitor), was previously investigated (Rennie et al., 2004). In this study, sensitivity for seizure detection by four trained neonatologists varied between 38% and 55%, depending on the speed of recordings (best results with 30 cm/h, namely less compressed tracings). Inter-observer agreement was also low. In this regard, the study by Frenkel et al. (2010) adds to our knowledge a comparison between non-expert performances with more experienced professional's skills, confirming the importance of expertise for the correct use of the method. Appart from the reader's expertise, another factor which probably contributed to improve seizure detection in the present study was the access to raw EEG. Importantly, when Shah et al. (2008) accessed concomitant raw EEG in their study, sensitivity for detecting seizure episodes increased from 56% to 76%.

Amplitude-integrated EEG is now a reality in many NICUs worldwide, and its virtues and limitations have been progressively growing in the last years. However, it is very important to assess the real role of this new technology in the management of at-risk babies and not to create unintended consequences by unwarranted interventions (Freeman, 2007). Therefore, we are not able to measure the real long-term outcome of undertreated subclinical seizures in neonates yet. Furthermore, overtreatment might have also unpredictable consequences. In the study by Frenkel et al. (2010), the non-expert reader found 6 times more seizures than the experienced interpreters. If the non-expert had to decide on treatment, at least 10 neonates would have received

unnecessary drugs. We can say that both under and overtreatment of seizure in neonates are two sides of the same coin.

Regarding outcome of neonatal seizures, in a recent randomized controlled trial studying the effect of treatment of subclinical seizures in neonates with hypoxic-ischemic encephalopathy, the authors found a trend for a reduction in seizure duration when clinical and subclinical seizures were treated. Also, there seems to exist a direct association between the duration of seizure and severity of the brain injury seen on MRI scan (van Rooij et al., 2010b). Further longitudinal studies, with long-lived outcomes, might confirm these data and clarify this issue.

Accordingly, a great effort must be made, especially regarding training of NICU's staff, before the implementation of aEEG as a tool for detecting signs of brain dysfunction in neonates. In addition, the medical community must be alert for the potential risks of overuse of this helpful new technology, because physicians should have in mind that they are treating human beings, not machines.

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10.2.   Arq Neuropsiquiatr 2011; 69: 565-6.

Topiramate is Effective for Status Epilepticus and Seizure Control in Neuraminidase Deficiency

Topiramato É Efetivo no Tratamento de Estado de Mal Epiléptico e Controle de Crises na Deficiência de Neuraminidase

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INTRODUCTION

Sialidosis, a rare lysosomal storage disorder is caused by a deficiency of the enzyme α-N-acetyl neuraminidase, resulting from mutations in the NEU1 gene.[1-5] Its main phenotypes are Sialidosis types I (milder form) and II (earlier onset).[1-5] Sialidosis type II is characterized by developmental delay, macular cherry-red spot, visceromegaly, coarse facies, dysostosis multiplex, and myoclonus.[1-5] We report a case of status epilepticus (S.E.) in a patient with Sialidosis type II which had good response to topiramate.

CASE REPORT

A 16 years-old girl was admitted to our emergency unit with S.E. She was using valproate 30 mg/Kg/day, primidone 10 mg/Kg/day, and clobazam 0.20 mg/Kg/day (maximum tolerated doses). Sialidosis type II was diagnosed nine years before, by detection of high levels of urinary sialil-oligossacharides, and deficient neuraminidase activity in leukocytes. Myoclonic seizures started at the age of eleven, and further became refractory to pharmacological treatment. Before admission, she was presenting weekly myoclonic seizures. She had neuropsychological delay, short stature, mild dysostosis multiplex, and a cherry-red spot on retinal exam. Intravenous midazolam was increased till 0.4 mg/kg/hour without any benefit. MRI revealed cerebellar and brain atrophy. Interictal EEG showed multifocal spikes, mainly involving bilateral parassagital regions. Seizures were easily provoked by tactile stimulus, and characterized by a extensor tonic spasm in four extremities, followed by tonic arms flexion and facial muscle contraction. These movements were followed by several massive generalized myoclonic jerks (Figure 1). Ictal EEG showed a train of 15 Hz

rhythmic spikes, predominantly in frontal regions, rapidly evolving to a polispike-slow wave complex with fast fading away, and replaced by a generalized depression of the background activity. Seizures occurred every 5 minutes, with total duration of 30 seconds. Valproic acid was increased to 75mg/Kg/day without benefit. Next day, we introduced topiramate 2.5 mg/Kg/day. There was improvement in seizure control, and 8 hours later patient was seizure-free. After discharge, she used this scheme for two years, with brief myoclonic jerks occuring in a monthly frequency.

DISCUSSION

Drugs used for treatment of S.E. are phenytoin, bezodiazepines, phenobarbital, and propofol.[1,2] , but treatment of S.E. in myoclonic progressive epilepsies is still not established. Midazolam was not effective here. Other options were propofol or barbiturates. Phenobarbital was already in use. Propofol is useful during acute phase but is not an option for long-term seizure control. Phenytoin could aggravate the myoclonic seizures of our patient. For the same reason, benzodiazepines would not be an option, because tonic seizures, a not uncommon type of seizure in the epileptic encephalopathies, could be originated by it. Newer agents (valproate, levetiracetam, or topiramate) might be an interesting option.[1] These drugs are also useful as antiepileptic drugs after S.E. Levetiracetam was not available to us. We tried topiramate and fortunately obtained a good response with a relatively low dosage. Then, we suggest topiramate for treatment of both, S.E. and seizures, in Sialidosis. Topiramate is possibly also a useful drug for other forms of progressive myoclonic epilepsies. Further studies are necessary to clarify these matters.

ACKOWLEDGMENTS

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10.3.   Clin Neurophysiol 2013; 124: 826-7.

Breach Effect Over Mitten Patterns Mimicking Focal Spike-Waves in a Patient with Psychogenic Nonepileptic Seizures

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Psychogenic nonepileptic seizures (PNES) resemble epileptic seizures. Video-EEG is the gold-standard diagnostic tool (Reuber, 2009). About 20% of patients with PNES are misdiagnosed as epileptics (Boesebeck et al., 2010), mainly by EEG overinterpretation (Benbadis and Tatum, 2003).

We saw a 48-years-old woman with spells since she was 14, taking three antiepileptic drugs (AEDs), and having three seizures by day on admission. An aneurysm was clipped 2 years before through a left frontotemporal craniotomy. We recorded a video-EEG, with the following technical parameters: time constant, 0.1s; high-frequency filter, 70 Hz; sensitivity, 10 µV/mm; page size, 10s. PNES were characterized by a motionless stare during 3 minutes. On sleep, breach effect over mitten patterns mimicked frontal spike-and-wave complexes (Figure 1).

Fig. 1 – EEG recorded in deep stages of sleep. Mitten patterns, mimicking left frontal spike-and-wave complexes. TC: 0.3 s; HFF: 70 Hz.
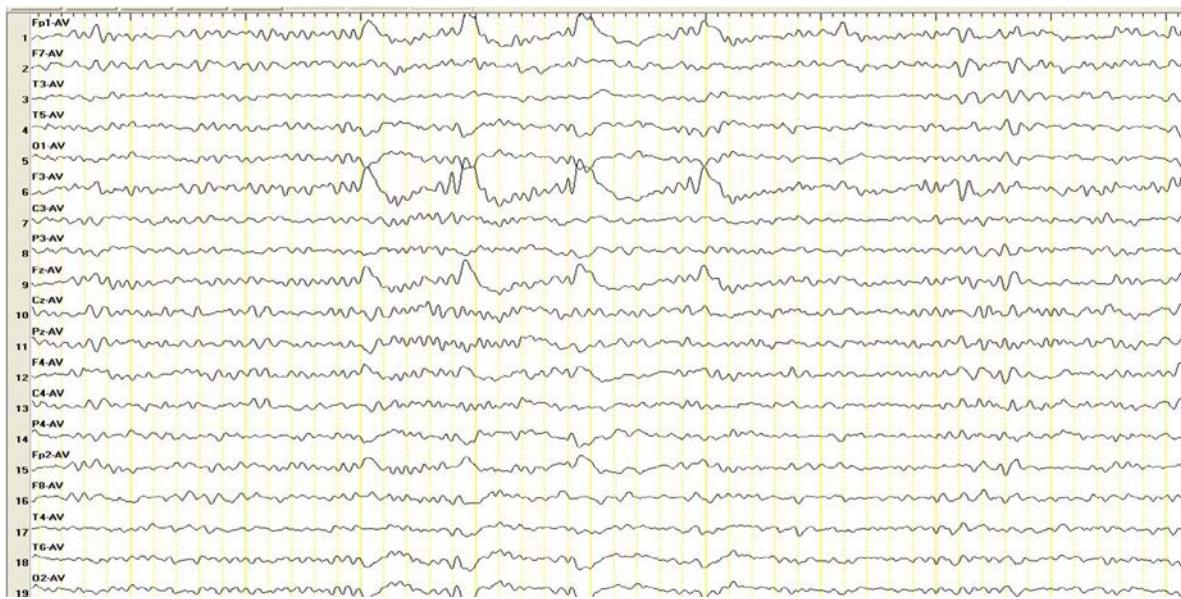
Normal variants, or benign variants of uncertain significance, are rhythmic or epileptiform patterns are often misinterpreted as an abnormal EEG. They possess some characteristics common to epileptiform patterns, and may reflect pitfalls for those interpreting EEGs (Benbadis and Tatum, 2003).

Mitten pattern, one of these normal variants, is a superimposition of a sharp wave on the slope of a slow wave with same polarity, centered in the frontal-central midline. With skull defects, non-epileptogenic activity may be misunderstood as pathologic discharges (Brigo et al., 2011). Breach effect over a mitten pattern is another benign epileptiform variant.

Overinterpretation of EEG may cause unnecessary medical (AED side effects) and financial consequences (Privitera, 2011). In this case, a peculiar normal variant influenced by a previous neurosurgical effect over EEG recording was misinterpreted as epileptiform. Physicians must be alert to possible pitfalls in the EEG interpretation, to avoid evil consequences to patients.

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10.4. Clin Neurophysiol 2013; 124: 1924.

Editorial

The Role of Triphasic Waves in the Care of Critically Ill Patients

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Triphasic waves (TWs) are a characteristic EEG pattern, and represent something more than a morphological description of wave. Initially described as "blunted spike and wave" (Foley et al., 1950), the term was further used to indicate rhythmic trains of bisynchronous and symmetric waves with a triphasic waveform that occur in adults with one of several pathologic conditions (Bickford and Butt, 1955), including other metabolic and toxic encephalopathies, sepsis-associated encephalopathy, and brainstem infarction (Kaplan and Rossetti, 2011), although they were initially considered to be pathognomonic of hepatic encephalopathy. TWs are thought to be associated with the thalamic mechanism as the network responsible generalized epilepdform discharges and/or the thalamocortical mediated spindle pathway (Karnaze and Bickford 1984, Sundaram and Blume 1987, Ogunyemi 1996).

Recently, with the advance in the use of continuous EEG monitoring of comatose patients, repeated waves with triphasic morphology, lateralized or generalized, was identified as one of ictal patterns found in non-convulsive status epilepticus (NCSE). Triphasic morphology of repetitive waves, in this scenario, is now considered merely a modifier term, not influencing on etiological issues (Hirsch et al., 2013). Differentiate NCSE form TWs of encephalopathy can be difficult, especially when the frequency of repetition of these waves is greater than 1/second (Kaplan, 1999). Lack of evolution in frequency, amplitude and distribution, an antero-posterior lag, reactivity to noxious stimuli, shorter duration of the wave's first component, extra-spike components and less generalized background slowing were all proposed as differentiating elements, but none of these criteria have been validated, and definitive conclusions are still lacking (Brigo and Storti, 2011).

The predictive value of TWs in adults with diffuse encephalopathies has been a matter of discussion for all those last years, with a special association between their presence and high mortality rate (Bahamon-Dussam et al., 1989; Sundaram and Blume, 1987). However, data in this regard have been provided by studies from more than two decades ago, and now it is time to review them.

In this issue of Clinical Neurophysiology, we have the opportunity to dwell again on this subject. Sutter and colleagues (Sutter et al., 2013) studied 105 adult patients with acute encephalopathy in a nine-year cohort. From clinical and EEG features, they hypothesized about prognostic factors for these patients.

Main results of this study were independent association between absent EEG reactivity and respiratory failure with death, both with high odds ratios respectively. However, mortality of patients in acute encephalopathy and TWs in their EEG was not so high as previously found, and, the most surprising, etiologies or underlying pathologies were not predictive for outcome for those patients. The authors raise many explanations for those new results found. Indeed, we might conclude that there is still a lot of work to do to clarify those and many other questions regarding the role of continuous EEG monitoring in the critically ill neurologic patient. And, as Sutter and colleagues showed to us (Sutter et al., 2013), we should not further just record EEG tracings, observing the infinite variability of EEG patterns of our patients. We must test and retest background EEG reactivity to many types of stimuli, because this is highly informative about the prognosis of comatose patients.

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11. CONSIDERAÇÕES FINAIS

A prevalência de transtornos psiquiátricos em pacientes com epilepsia do lobo temporal, no nosso meio, é bastante elevada. Cerca de metade dos nossos pacientes apresenta ou apresentou ao menos um diagnóstico de transtorno mental ao longo da vida. Em cerca de 40% deles, havia mais de um diagnóstico psiquiátrico, mais frequentemente uma associação de depressão com ansiedade. História familial psiquiátrica positiva e presença de descargas interictais no EEG envolvendo o hemisfério esquerdo são fatores de risco independentes para um diagnóstico de transtorno de humor entre os pacientes com epilepsia do lobo temporal. Considerando que comorbidades psiquiátricas têm impacto direto no prognóstico de pacientes epilépticos, influenciando o controle farmacológico e cirúrgico de crises, e aumentando a mortalidade, é fundamental a identificação destas variáveis clínicas durante a avaliação diagnóstica dos pacientes com ELT.

O nosso estudo demonstrou a influência direta de polimorfismos de genes ligados ao sistema serotoninérgico sobre a presença de transtornos psiquiátricos nos pacientes com ELT. Outros fatores de risco independentes também se mostraram importantes, sobretudo no transtorno de adição ao álcool, como sexo, história familial para epilepsia e para transtornos psiquiátricos. Acreditamos ser esse um importante elemento do sistema neurotransmissor a ser estudado futuramente em pacientes com epilepsia.

Cabe ainda ressaltar que a neurofisiologia continua desempenhando papel fundamental no estudo e manejo dos pacientes com epilepsia. Este trabalho observou uma associação inversa entre a frequência de descargas interictais e a presença de sintomas depressivos nos pacientes com ELT, um

plausível correlato neurofisiológico de fenômenos complexos que caracterizam a associação entre as duas doenças, como é o fenômeno da Normalização Forçada.

Com o avanço do conhecimento em Neurociências, e com o surgimento progressivo de novas ferramentas diagnósticas, abre-se uma perspectiva promissora para um entendimento cada vez maior dos transtornos neuropsiquiátricos.