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EPILEPSIA DE LOBO TEMPORAL FAMILIAL: CARACTERIZAÇÃO DA EVOLUÇÃO NATURAL, PROGRESSÃO DA ATROFIA HIPOCAMPAL E RESPOSTA AO TRATAMENTO.

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.

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"*A verdadeira viagem do descobrimento não consiste em procurar novas paisagens, mas em ver com novos olhos."* (Marcel Proust)

Resumo

RESUMO

Introdução: A epilepsia de lobo temporal mesial (ELTM), a principal causa de epilepsia parcial no adulto, está freqüentemente associada à atrofia hipocampal (AH). O conhecimento sobre sua história natural e fisiopatologia é baseado predominantemente em séries cirúrgicas. A ELTM familiar (ELTMF) é caracterizada pela recorrência em uma mesma família de indivíduos com ELTM com diversos graus de gravidade. Este aspecto, associado ao fato de alguns membros assintomáticos apresentarem sinais de AH na RM, faz com que o estudo prospectivo da ELTMF seja o cenário ideal para o melhor entendimento da história natural e fisiopatologia da ELTM.

Materiais e Métodos: Analisamos prospectivamente 103 indivíduos pertencentes a 17 famílias com ELTMF. O tempo de seguimento foi em média 7,6 anos (SD ± 1,8 anos). Os membros das famílias foram divididos em três grupos: ELTMF (n=53), não classificáveis (crises que não preenchiam critérios para ELTM; n=18) e assintomáticos na primeira avaliação (n=32). O grupo com ELTMF foi subdividido em subgrupos: remissão (n=19), benignos (n=17) e refratários (n=17). Posteriormente o grupo com ELTMF foi reclassificado de acordo com sua evolução clínica em favorável e desfavorável. As evoluções clínicas foram correlacionadas com os possíveis fatores prognósticos. Sinais de AH na MRI foram definidos por análise visual. Em um estudo paralelo, foi feita a volumetria manual do hipocampo nas duas imagens de RM quando disponíveis.

Resultados: No grupo benigno os pacientes evoluíram ou para refratariedade (17,6%) ou para remissão (23,5%). No grupo inicialmente em remissão, a maioria dos pacientes permaneceu em remissão e 21% foram reclassificados como benignos. Todos os

pacientes refratários permaneceram refratários, exceto quando submetidos à cirurgia. Dos assintomáticos 12,5% desenvolveram ELTMF benigna e do grupo não classificáveis 22% evoluíram para o diagnóstico de ELTMF benigna. Foram considerados fatores preditivos relacionados à evolução clínica desfavorável a presença de AH (p=0,0192) e atividade epileptiforme no EEG (p=0,0174). A correlação entre incidentes precipitantes iniciais e evolução clínica não foi significativa, porém, uma clara tendência (p=0,0549) foi observada. Em relação à volumetria observamos progressão da atrofia quando comparamos o volume da RM inicial com a última RM.

Discussão: Os resultados observados confirmam o caráter geralmente benigno da ELTMF. Este achado ressalta a existência de pacientes que mesmo na presença de sinais de AH apresentam uma evolução favorável, colocando em questão o conceito tradicional de que a ELTM com AH seria necessariamente refratária. Além disso, a demonstração da existência de fatores preditivos de má evolução clínica corrobora a hipótese de que outros fatores, além da influência genética, também estariam envolvidos na fisiopatologia desta doença. Em relação à progressão da ELTMF, dados de volumetria reforçam a teoria de que a ELTM seria uma doença progressiva, cuja velocidade de seu curso poderia ser influenciada por fatores externos. Este estudo longitudinal trouxe dados adicionais sobre a história natural da ELTMF que reforçam e clareiam algumas das hipóteses previamente formuladas. O melhor entendimento dos mecanismos subjacentes a ELTMF é importante para determinar estratégias terapêuticas visando melhor controle de crises e talvez, assim, prevenindo epileptogênese e progressão de dano neuronal.

Palavras-chave: Ressonância Magnética, Epilepsia do Lobo Temporal Mesial, Neuroimagem, Estudo Longitudinal

Abstract

ABSTRACT

Introduction: Mesial temporal lobe epilepsy (MTLE), the main cause of partial epilepsy in adulthood, is frequently associated with hippocampal atrophy (HA). The knowledge regarding its natural history and pathophysiology is based mainly on surgical series. Familial mesial temporal lobe epilepsy (FMTLE) is characterized by the recurrence of MTLE in the same family with different degrees of severity. This aspect, together with the fact that some asymptomatic members have MRI signs of HA, makes the prospective study of FMTLE the perfect scenario for the better understanding of the natural history and pathophysiology of MTLE.

Material and Methods: We analyzed prospectively 103 individuals belonging to 17 families with FMTL. The mean duration of follow up was 7.6 years (SD, ± 1.8 years) Family members were divided into 3 groups: FMTLE (n=53), unclassified (seizures that did not fulfill criteria for MTLE, n=18) and asymptomatic at first evaluation (n=32). The FMTLE group was divided into 3 subgroups named: remission (n=19), benign (n=17) and refractory (n=17) and were further reclassified according to their outcome in favorable outcome and poor outcome. Outcome groups were correlated with possible predictor factors. MRI signs of atrophy were defined by visual analysis. In a related study, we performed manual volumetry in both MRI images when they were available.

Results: In the benign group patients evolved to either refractoriness (17.6%) or remission (23.5%). In the remission group, most patients remained seizure free and only 21% were further reclassified as benign. All refractory patients remained refractory or underwent surgery. From the asymptomatic group 12.5% developed benign FMTLE and

from the unclassified seizure group 22% evolved to a diagnosis of benign FMTLE. Predictive factors related to poor outcome were presence of HA (p=0.0192) and interictal epileptiform discharges on EEGs (p=0.0174). The correlation between initial precipitating injuries and clinical outcome was not significant although a clear tendency was observed (p=0.0549). Regarding volumetric analysis, when comparing hippocampal volumes from initial and last MRIs, we observed progression of HA.

Discussion: Our results confirm the benign aspect of FMTLE. This finding emphasizes the existence of patients with good outcome even in the presence of signs of HA, challenging the notion that MTLE with HA is always refractory. Furthermore, the demonstration of predictive factors of poor clinical outcome supports the hypothesis that, in addition to the genetic influence, there should be other factors involved in the pathophysiology of this condition. Volumetric data reinforces the theory that MTLE might be a progressive disorder, and that the rate of progression would be influenced by external factors. This longitudinal study brought additional data regarding the natural history of FMTLE that strengthens and clarifies some of the previously formulated hypotheses. The better understanding of the underlying mechanisms of FMTLE is important to determine therapeutic strategies aiming better seizure control and perhaps thereby preventing epileptogenesis and progression of neuronal damage.

Key-words: Magnetic Resonance, Mesial temporal lobe epilepsy, Neuroimage, Longitudinal study.

AE	Atividade Epileptiforme
AH	Atrofia hipocampal
CA	Corno de Amon
CFs	Crises febris
CTCG	Crise tônico-clônica generalizada.
DAE	Drogas anti-epilépticas
EEG	Eletroencefalograma
EH	Esclerose hipocampal
ELT	Epilepsia de lobo temporal
ELTL	Epilepsia de lobo temporal lateral
ELTM	Epilepsia de lobo temporal mesial
ELTMF	Epilepsia de lobo temporal mesial familiar
FLAIR	*Fluid attenuated inversion recovery*
FOV	*Field of view* (campo de visão).
ILAE	*International League Against Epilepsy*
IPIs	Insultos precipitantes iniciais
MBV	Morfometria Baseada em voxel
NAA	N-acetil-aspartato
PET	*Positron Emission tomography*
RM	Ressonância Magnética
SPECT	*Single photon emission computed tomography*
TCE	Traumatismo crânioencefálico

T Tesla. É a unidade de densidade de fluxo magnético (ou indução magnética) no SI. A unidade recebeu o nome de Nikola Tesla, cientista sérvio que contribuiu com inúmeros estudos no campo do eletromagnetismo. 1 T = 10.000 G (Gauss, unidade antiga de medida de campo magnético).

T1 Tempo de relaxamento longitudinal, parâmetro utilizado na realização em exames de imagens por RM. Corresponde ao tempo necessário para que a magnetização longitudinal retorne a 63% de seu valor inicial.

T2 Tempo de relaxamento transversal, parâmetro utilizado na realização em exames de imagens por RM. Corresponde ao tempo necessário para que a magnetização transversal diminua de 63%.

TE Tempo de eco: duração entre o pulso e a recepção do sinal de ressonância magnética.

TR Tempo de repetição: duração do intervalo entre os trens de impulso em alta frequência.

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Introdução

INTRODUÇÃO

A epilepsia afeta aproximadamente 1-2% da população mundial com uma prevalência variando de 5-10/1000 na maioria dos locais (1, 2). Ela pode ser classificada em generalizada ou parcial. A epilepsia de lobo temporal mesial (ELTM) é o tipo mais frequente de epilepsia parcial do adulto, estando frequentemente associada à esclerose hipocampal (EH) e à refratariedade a drogas antiepilépticas (DAE). É também a principal indicação de cirurgia de epilepsia (3).

A história natural de uma doença descreve o seu curso desde o início até seu desfecho. Neste sentido, existe uma lacuna no conhecimento sobre a história natural da ELTM, uma vez que ele é baseado principalmente em estudos de séries cirúrgicas, ou seja, reflete predominantemente o desfecho de um grupo específico de pacientes, os refratários ao tratamento com DAEs (3).

A ELTM não parece seguir um modelo fixo de evolução. Em relação aos casos refratários, sabe-se que as crises têm início geralmente na infância ou adolescência, apresentando muitas vezes um período de bom controle de crises que precede a refratariedade. Esse período é conhecido como período latente e pode também ser observado em alguns modelos experimentais (ex. modelo da pilocarpina) (4).

Após instalação da refratariedade, alguns pacientes apresentam períodos breves de remissão intercalados com recorrência de crises (remissão-recidiva), entretanto, a maioria permanece refratária durante o curso da doença (5). Não se sabe, contudo, o que determina tal refratariedade, especialmente porque os casos com boa evolução clínica

acabam por perder seguimento. A falta de estudos de pacientes com boa evolução clínica determina uma importante lacuna no conhecimento atual sobre a ELTM (6).

Alguns possíveis fatores prognósticos relacionados à refratariedade foram sugeridos por estudos retrospectivos de séries cirúrgicas, entre eles: presença de crises febris (CFs), presença de atrofia hipocampal (AH), início precoce das crises e presença de anormalidades interictais no eletroencefalograma (EEG) (7).

A EH é a principal lesão associada à ELTM. É caracterizada por perda neuronal e gliose envolvendo os setores hipocampais CA1, CA3 e hilo do giro denteado (CA4) e poupando relativamente CA2, o *subiculum* e o giro denteado (8).

A ressonância magnética (RM) é o padrão ouro na detecção *in vivo* da EH na ELTM. As principais anormalidades encontradas são AH, perda da arquitetura interna do hipocampo, hipersinal em imagens ponderadas em T2 e hipossinal em T1 (8). A RM é, dessa forma, uma excelente ferramenta na investigação *in vivo* das questões relacionadas à EH. Os termos AH e EH são frequentemente utilizados como sinônimos, porém indicam conceitos diferentes, sendo a AH um dos aspectos da EH. No decorrer desta tese, utilizaremos o termo AH para indicar alterações relacionadas ao volume do hipocampo, e o termo EH para o conceito da patologia como um todo.

A relação entre crises e EH já é estudada há mais de 150 anos (9). Desde as primeiras descrições, foi levantada a questão se a EH seria causa ou consequência das crises (10). Esse ainda é um tema controverso e, assim como em muitas outras questões biológicas, a resposta deve estar entre esses dois extremos.

Baseando-se nesta questão, nosso centro (11) publicou em 2001 uma série de 98 indivíduos pertencentes a famílias que apresentavam pelo menos dois indivíduos com diagnóstico de ELTM. Desses, 68 apresentavam diagnóstico de epilepsia de lobo temporal mesial familiar (ELTMF). Tal estudo permitiu uma análise das alterações hipocampais através de exames de RM no contexto de uma mesma influência genética.

A caracterização clínica desses pacientes mostrou que dentro de uma mesma família podem ocorrer diversas manifestações clínicas, como membros com crise única, indivíduos com evolução benigna e pacientes com crises refratárias (11). A RM detectou AH em 57% desses pacientes, inclusive em membros com quadros benignos e naqueles que não preenchiam critérios para ELTM. Além disso, foram avaliados 52 indivíduos assintomáticos e, desses, 18 (34%) apresentaram sinais de EH (12). Estes achados falam contra a possibilidade da EH ser apenas consequência de crises.

Considerando, então, que a EH seria a causa das crises, o que causaria a EH? A presença de indivíduos assintomáticos com AH mostra que ela não está necessariamente relacionada à gravidade das crises e sugere a importância da predisposição genética na gênese da EH na ELTMF. Devem existir, no entanto, outros cofatores que, associados ou não à predisposição genética, influenciariam na gênese da EH.

Estudos epidemiológicos mostraram que em pacientes com EH há uma maior incidência de insultos precipitantes iniciais (IPIs), como, por exemplo, história na infância de traumatismo cranioencefálico (TCE), *status epilepticu*s, complicações perinatais e CFs (13). Esses fatores também parecem estar envolvidos na gênese da EH (14).

Surge então uma terceira pergunta: Será que as crises poderiam piorar a EH? Ou melhor, será que existiria progressão da EH?

Alguns estudos sugerem que há progressão de AH com o passar do tempo e que crises recorrentes podem resultar em mudanças progressivas na função e estrutura do hipocampo (8, 15, 16). Ainda há, no entanto, controvérsias em relação aos fatores que influenciam tal progressão (14).

Não há na literatura estudos prospectivos descrevendo a história natural ou possíveis preditores de evolução clínica na ELTMF. A presença de indivíduos em uma mesma família com diferentes padrões de frequência de crises e resposta às DAEs faz com que o estudo prospectivo da ELTMF seja o cenário ideal para o melhor entendimento da história natural e fisiopatologia da ELTM e da EH.

Dentro deste contexto, realizamos uma análise longitudinal de uma coorte de indivíduos pertencentes a famílias com ELTMF já estudas previamente buscando responder as seguintes questões: Qual é a história natural da ELTMF? Quais fatores influenciam as diferentes evoluções clínicas? Há progressão de AH com o passar do tempo?

A melhor compreensão dos mecanismos subjacentes será importante para determinar estratégias terapêuticas visando melhor controle das crises, talvez, assim, prevenindo epileptogênese e progressão de dano neuronal (14). Estudos longitudinais utilizando imagens de RM auxiliariam na elucidação desta questão.

Revisão da Literatura

REVISÃO DA LITERATURA

1. Epilepsia de lobo temporal (ELT)

O termo ELT tem sido utilizado para descrever crises parciais complexas (CPC) de provável origem no lobo temporal.

O quadro clínico da ELT foi inicialmente descrito por Hughlings Jackson em 1876. Suas descrições foram baseadas em relatos detalhados feitos por um de seus pacientes que era médico. Ao descrever o chamado "*dreamy state*", ele caracterizou com perfeição os sintomas típicos de uma crise de lobo temporal. Posteriormente, por volta de 1894, após autopsia desse mesmo paciente, ele fez pela primeira vez a associação das crises descritas com a possível origem no lobo temporal (17).

Ainda hoje, as informações semiológicas relacionadas às crises são fundamentais no diagnóstico da ELT, fazendo parte dos critérios diagnósticos dessa patologia (18).

A ELT pode ser dividida em ELTM ou epilepsia de lobo temporal lateral (ELTL) de acordo com a origem nas estruturas mesiais ou neocorticais do lobo temporal (19).

A ELTM é a forma mais frequente. Representa a maior parte das ELT, estando frequentemente associada à EH (18). Já a ELTL pode ou não apresentar lesão neocortical visível (20, 21). Ambas as formas de ELT podem ocorrer de forma esporádica (não familiar) ou familiar.

2. Epilepsia de lobo temporal mesial

O diagnóstico da ELTM baseia-se na somatória de achados clínicos e laboratoriais. Isoladamente nenhum critério é suficiente para o diagnóstico da ELTM. No entanto, quanto maior o número de critérios combinados, maior a certeza diagnóstica (18).

O diagnóstico baseia-se principalmente nos seguintes critérios:

- Semiologia típica de crises de lobo temporal;

- Presença de alterações eletroencefalográficas ictais e interictais na região temporal média ou anterior-médio basal;

- Ocorrência de sinais de AH na RM;

- Presença de alterações específicas da memória na avaliação neuropsicológica;

- Presença de resultados de outros exames sugestivos de início das crises no lobo temporal (por exemplo, PET e SPECT).

Algumas características falam contra o diagnóstico de ELTM, como por exemplo, presença de atividade epileptiforme extra-temporal, aura sugestiva de início em outras áreas que não o lobo temporal, alterações cerebrais difusas na neuroimagem ou presença de déficits neurológicos focais.

2.1 Manifestações clínicas da ELTM

Do ponto de vista clínico, os pacientes apresentam crises parciais simples (CPS), CPC ou ambas, com características sugestivas de início em lobo temporal (sensação epigástrica ascendente, medo, *déjà-vu*, *jamais-vu*). Crises tônico-clônicas generalizadas (CTCG) podem ocorrer, porém são incomuns após introdução de DAE. Nesses pacientes são frequentes os antecedentes de CFs na infância, TCE, presença de crises prolongada, problemas perinatais ou infecção de sistema nervoso central, também conhecidos como IPIs. Supõe-se que os IPIs estejam envolvidos na gênese da ELTM (18).

A primeira crise "habitual" ocorre geralmente entre quatro e 16 anos, podendo ocorrer mais precoce ou tardiamente. Entre a primeira crise e o início das crises refratárias, muitas vezes é relatado um período silente. Após instalação da refratariedade, a cirurgia de epilepsia torna-se a melhor opção de tratamento principalmente nos casos associados à AH unilateral (4, 18).

Tradicionalmente, a ELTM com EH foi sempre vista como uma doença adquirida, refratária e associada a CFs. Estudos sugerem que apenas 11 a 25% dos pacientes com sinais de AH na RM terão boa resposta ao tratamento medicamentoso (22). No entanto, essas conclusões são baseadas em séries cirúrgicas e podem não representar a real história natural da ELTM.

Até hoje, pouca atenção foi dada a quadros mais benignos de ELTM. Estudos mais recentes de pacientes com ELTM não selecionados para cirurgia sugerem a existência de indivíduos com ELTM e sinais de AH que apresentam uma evolução clínica mais benigna (6, 23). Esse achado é importante, pois muda a visão que tradicionalmente temos em relação à ELTM e à refratariedade. Sugere que conclusões relacionadas à presença

isolada de AH na RM e controle de crises a longo prazo devem ser feitas com cautela, já que não existem estudos prospectivos na literatura avaliando esse grupo benigno de pacientes.

3. Anatomia do Hipocampo

O hipocampo é uma estrutura localizada na região mesial do lobo temporal. Tem este nome pela sua semelhança com um cavalo marinho (Grego: *hippos* = cavalo, *kampi* = curva). É constituído por duas camadas corticais: o corno de Amon (CA) e o giro denteado (*fascia dentata*). Estas camadas são separadas pelo sulco hipocampal e cobertas pela fimbria e alveus. Histologicamente o CA é dividido em sub-regiões (CA1, CA2, CA3 e CA4). A região CA4 é também conhecida como *endofolium* ou hilo da *fascia dentata*. O giro denteado é constituído por três camadas: *stratum granulosum*, *stratum moleculare* e camada polimórfica. A *area dentata* é composta pela região CA4 e giro denteado (Figura 1) (24).

Por muito tempo o hipocampo foi o principal foco enfatizado ELT. No entanto nova ênfase foi dada a várias estruturas extra-hipocampais que também estão alteradas na ELT. Entre elas a amígdala, o córtex entorrinal, o córtex peririnal e córtex para-hipocampal. Estudos mostraram que tais estruturas parecem estar envolvidas na gênese e propagação das crises. Em estudos anatomopatológicos foi detectada perda neuronal na região para-hipocampal, particularmente no córtex entorrinal (15).

Figura 1. Anatomia do hipocampo

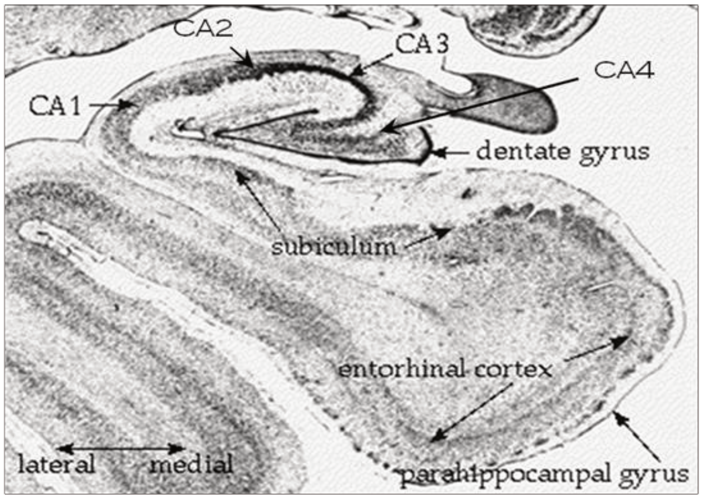

Figura 1. Neste corte coronal podemos observar detalhes da anatomia do hipocampo e de algumas regiões extra-hipocampais. Legenda: *Dentate gyrus*, giro denteado; *entorhinal córtex*, córtex entorrinal; *parahippocampal gyrus*, giro para-hipocampal.

4. Esclerose hipocampal

A EH foi inicialmente descrita em 1825 por Bouchet e Cazauvieilh como um achado anatomopatológico *post-mortem* encontrado em pacientes com epilepsia e "insanidade". Inicialmente foi dada pequena importância a tal achado. Foi em 1880 que Sommer reconheceu a importância da EH em pacientes com epilepsia (4, 25).

O termo esclerose vem do grego *sklerósis* = "endurecimento" e refere-se à descrição macroscópica de um hipocampo com volume reduzido e endurecido. Histologicamente EH refere-se a uma perda neuronal seletiva do hipocampo. Há áreas

mais vulneráveis à lesão como os setores CA1, CA3 e CA4 *(endofolium*) e áreas com uma relativa preservação como as células granulares do giro denteado, setor CA2 e *subiculum* (9).

Desde as primeiras descrições, foi levantada a questão se a EH seria causa ou consequência das crises (10, 25).

Inicialmente a distribuição heterogênea da EH, com áreas mais afetadas que outras, foi vista como consequência de uma vascularização específica para os diferentes setores do hipocampo e levantou a questão sobre a possível causa vascular/isquêmica da EH. Vogt (1925) acreditava que as diferentes características físico-químicas dos setores do hipocampo levariam a diferentes áreas de vulnerabilidade explicando assim a heterogeneidade da lesão (9).

Com o reconhecimento da importância dessa lesão na ELT, a EH foi então considerada causa da epilepsia. Tal teoria ganhou força principalmente após o aumento progressivo de estudos de tecidos provenientes de paciente com ELT submetidos à ressecção do hipocampo para tratamento de epilepsia.

Alguns achavam que a EH poderia ser consequência de insultos pós-isquêmicos do período perinatal (como herniação da artéria cerebral posterior durante o parto) (9).

Em 1968 Falconer e Taylor desenvolveram um conceito mais moderno de que a EH seria tanto causa como consequência de crises. Assumiram que crises durante a infância poderiam gerar modificações nas estruturas mesiais temporais que resultariam em EH e estudos utilizando métodos morfométricos de materiais provenientes de cirurgia apoiaram a visão de que a EH seria a causa das crises. Simultaneamente, alguns achados mostraram

que crises podem alterar a patologia hipocampal (principalmente no *endofolium* e *fascia dentata*). Dessa forma, EH seria tanto causa como consequência de crises (9).

Vários outros estudos de autopsia mostraram que a frequência de EH em pacientes com ELT era muito maior que em outros tipos de epilepsia, enfatizando a importância da EH na gênese da ELT.

Considerando então a EH clássica com alterações predominantemente na região CA1 como fator causal da ELT e alterações no *endofolium* e *stratum granulosum* (uma das camadas do giro denteado) como consequência das crises, indicando plasticidade e progressão da doença fica ainda a dúvida: Qual seria o insulto primário responsável pela EH? Quais seriam os mecanismos responsáveis pela epileptogênese e progressão da doença? Que fatores tornariam o hipocampo suscetível (9)?

Hoje se acredita que distúrbios no desenvolvimento do hipocampo possam torná-lo mais vulnerável (9).

Alguns estudos mostraram que nos pacientes com epilepsia e EH há uma redução da inibição e um aumento da excitação neuronal. Morfologicamente isso pode ocorrer por perda neuronal e reorganização das fibras musgosas com criação de novas sinapses. Esse desequilíbrio inibitório-excitatório poderia ser responsável pelo caráter epileptogênico da lesão (9, 26, 27).

Desde 1965, a importância da neuroglia na epilepsia tem sido um tópico em discussão. A contribuição das células gliais para epileptogênese é sustentada pelo aumento progressivo de dados sobre o papel da inflamação e dos distúrbios na barreira hematoencefálica nas epilepsias progressivas (28).

Em conclusão, os fatores morfológicos e moleculares da suscetibilidade a crises na ELT com EH são caracterizados por uma vulnerabilidade seletiva neuronal associada a mudanças nas redes neuronais, com proliferação neuronal errônea e desbalanço das células gliais. As lesões resultantes e os mecanismos de adaptação e reorganização são provavelmente parte do processo de epileptogênese que poderia ocorrer durante o período latente (entre o insulto primário e o início das crises) ou poderia ser um processo progressivo. Não se sabe, no entanto, quais seriam os mecanismos envolvidos e responsáveis por tal processo.

5. Progressão da atrofia hipocampal

Apesar de controvérsias em relação à recorrência de crises e progressão de atrofia em epilepsia, estudos sugerem que crises recorrentes podem resultar em mudanças progressivas na função e estrutura do hipocampo (8, 15).

Experimentos indicam que crises podem induzir plasticidade cerebral que pode ser tanto deletéria quanto protetora, podendo promover tanto um mecanismo adaptativo homeostático que protegeria o cérebro de danos adicionais, quanto a indução de dano neuronal cumulativo e aumento da susceptibilidade à sincronização da rede neuronal.

A presença de alterações de memória em pacientes com ELT com EH já foi claramente demonstrada. Dados clínicos sugerem que o início precoce de crises e a epilepsia de longa duração estão associados a um pior desempenho nos testes

neuropsicológicos (14, 15). Ainda há, no entanto, controvérsias em relação à influência da frequência de crises na progressão da AH (14).

Estudos mostram que a presença de EH não está necessariamente relacionada à gravidade das crises e que pode estar presente em pacientes que nunca apresentaram crises (12). Existem relatos de alterações específicas da memória em avaliações neuropsicológicas de pacientes assintomáticos com EH (29). Tal achado fortalece ainda mais a hipótese de que a EH na ELTM seja determinada por uma forte predisposição genética (12).

6. Epilepsias familiares

Desde 400 a.C. Hipócrates já suspeitava da base genética da epilepsia (30). Quando discutimos a possibilidade da EH ser a causa da ELT retornamos à pergunta feita anteriormente: Qual seria o insulto primário responsável pela EH? Ou melhor, o que causaria a EH? Ao tentar responder essa pergunta, a influência genética é um fator que não poderia ser esquecido.

O estudo de famílias com história recorrente de indivíduos com epilepsia permitiu a descoberta de alguns tipos de epilepsia ligados a mutações genéticas. Dentre elas foram identificados, por exemplo, a epilepsia de lobo frontal noturna autossômica dominante (ligação com os cromossomos 20q, 1q e 15q) (31-33), epilepsia parcial com foco variável (ligada ao cromossomo 22q) (34), epilepsia rolândica (cromossomo 15q) (35) e as ELT familiares (30, 36).

Em pacientes com história de recorrência familiar, a caracterização clínica detalhada dos membros afetados é fundamental para definir os diferentes tipos de síndromes epilépticas familiares.

Pacientes com recorrência familiar de epilepsia podem apresentar epilepsia generalizada com crises febris (GEFS+) (37), epilepsia parcial familiar com foco variável (FPEVF) (38), epilepsia de lobo temporal com características auditivas (39) e ELTMF (18).

7. Epilepsia de lobo temporal familiar

A ELT familiar pode ser dividida em dois tipos: a ELTMF e a ELTL com aura auditiva também conhecida como epilepsia parcial autossômica dominante com aura auditiva (18).

7.1. Epilepsia de lobo temporal lateral com auras auditivas

A ELTL com auras auditivas é uma forma benigna de ELT familiar caracterizada pela presença de crises precedidas por fenômenos auditivos e atividade epileptiforme na região temporal posterior. Algumas vezes afasia ictal e percepção visual alterada também já foram descritas. O padrão de herança observado foi o autossômico dominante com penetrância incompleta. Este tipo de epilepsia foi ligado à mutação do gene LGI-1 (40, 41).

7.2. Epilepsia de lobo temporal mesial familiar

A ELTMF é considerada um subgrupo de ELT (18) e foi inicialmente descrita por Berkovic *et al* (42). É caracterizada pela recorrência familiar de ELTM em pelo menos dois indivíduos parentes de primeiro ou segundo grau com critérios clínico e eletroencefalográficos de ELTM de acordo com os critérios da ILAE (19) e pela ausência de sintomas e/ou sinais sugestivos de outras epilepsias parciais ou generalizadas nos outros membros afetados da mesma família. A semiologia e investigação clínica dessas famílias são semelhantes aos casos de ELTM esporádicos.

A comparação dos achados histológicos de hipocampos de pacientes refratários com história familiar e esporádica foi semelhante, exceto pelo fato de pacientes com quadro familiar apresentarem reorganização de fibras musgosas (*mossy fiber sprouting*) menos pronunciada que nos pacientes esporádicos. Tal achado sugere que a resposta a modificações neuronais nos casos familiares é diferente da que ocorre nos casos esporádicos (43).

A ELTMF foi inicialmente descrita como benigna, porém investigações subsequentes demonstraram um padrão variável em termos de gravidade de crises (11, 36) com ocorrência de casos refratários de ELTMF (inclusive cirúrgicos). A maioria dos pacientes, no entanto, apresenta um bom controle de crises.

A observação de um padrão de herança, que parece ser autossômico dominante com penetrância incompleta, implica na existência de portadores assintomáticos que poderiam transmitir as alterações genéticas associadas à ELTMF para seus descendentes (44). Foi sugerido também um modelo multifatorial para epilepsia em que haveria uma interação de um ou mais genes com fatores ambientais. (padrão de herança complexo) (45).

As anormalidades hipocampais, apesar de mais acentuadas em pacientes com crises refratárias (46), também são encontradas em membros assintomáticos e naqueles com bom controle de crises. Tal achado é um forte indicativo da importância dos fatores genéticos na gênese da ELTMF (12).

8. Neuroimagem

A neuroimagem é a principal ferramenta utilizada para detecção *in vivo* da EH. Novas tecnologias, incluindo RM de alta resolução, espectroscopia e outros estudos com ressonância funcional têm ampliado o nosso conhecimento relacionado à EH e sua progressão.

8.1. Análises qualitativas

A avaliação visual das imagens de RM deve ser realizada utilizando protocolos específicos de aquisição de RM que contenham cortes coronais finos e imagens ponderadas em T2 ou imagens FLAIR, para análise de alterações do sinal.

A análise visual é a técnica clinicamente mais utilizada para detecção *in vivo* de sinais de EH. É, porém, dependente da experiência do analisador. Dessa forma, a utilização de medidas volumétricas do hipocampo tem se mostrado mais específica e sensível para a detecção de AH (8).

8.2. Análises quantitativas

Existem algumas técnicas de neuroimagem que podem ser utilizadas para quantificar as modificações ocorridas na RM de pacientes com EH, auxiliando no melhor conhecimento sobre esta patologia. O volume das estruturas cerebrais (hipocampo e outras estruturas) pode ser, por exemplo, quantificado de forma manual, semiautomática ou automática nas imagens de RM. Outras modalidades de imagem (como PET e SPECT) também podem ser corregistradas a imagens estruturais fornecendo informações adicionais sobre a ELTM.

Os estudos volumétricos, por gerarem dados numéricos, permitem a comparação do grau de atrofia com diversos parâmetros clínicos. Estudos transversais mostraram uma associação entre grau de atrofia e duração da epilepsia (47, 48). Esses estudos, no entanto, apresentam limitações em relação às conclusões inferidas a partir de seus resultados. Estudos longitudinais seriam necessários para superar estas limitações.

A quantificação do sinal em imagens ponderadas em T2 (relaxometria) parece se correlacionar com sinais de gliose e não parece estar diretamente relacionada ao grau de perda neuronal (49, 50).

A análise de textura do hipocampo (avaliação do grau de modificação dos tons de cinza) é um método utilizado para detectar e quantificar as anormalidades estruturais em diferentes tecidos. Neste contexto, permite detectar modificações sutis na RM. Estudos prévios mostraram alterações na textura do hipocampo de pacientes com ELTM, inclusive no hipocampo contralateral (51, 52).

A morfometria baseada em voxel (MBV) permite a comparação voxel a voxel de diferentes grupos utilizando imagens em 3D. A MBV realiza uma comparação estatística da concentração (ou volume relativo) de substancia cinzenta, branca ou líquor de forma totalmente automática (53). Estudos recentes mostram que, em pacientes com ELTM, há uma redução da concentração de substância cinzenta que se estende além do hipocampo, envolvendo estruturas corticais e subcorticais conectadas às estruturas mesiais do lobo temporal (54, 55).

Em doenças degenerativas caracterizadas por perda neuronal, uma redução do N-acetil-aspartato (NAA) é frequentemente detectada por espectroscopia. Como o NAA é encontrado nos neurônios e não nas células gliais, ele é considerado um marcador de perda ou disfunção neuronal. Estudos utilizando a espectroscopia mostraram redução focal do sinal do NAA em pacientes com diferentes formas de ELT, incluindo pacientes com RM normal à análise visual (56).

Em resumo, a neuroimagem é hoje fundamental na investigação de diversas patologias do SNC. O uso dessa ferramenta em imagens adquiridas de forma prospectiva pode elucidar algumas das dúvidas relacionadas à história natural da ELTM e EH.

A maioria dos estudos realizados até hoje foram estudos seccionais. Estudos longitudinais utilizando técnicas de neuroimagem *in vivo* são muito mais adequados para a análise da questão causa e consequência da EH.

Os apêndices 7, 8 e 9 são revisões da literatura relacionadas à ELTMF e à EH publicadas durante o doutorado.

9. Justificativa

Nosso grupo identificou a ocorrência de EH em RM de indivíduos assintomáticos parentes de primeiro e segundo grau de pacientes com ELTMF (11, 12). Esse dado é fundamental na compreensão da origem da EH. O presente estudo tem por objetivo avaliar a proporção de indivíduos, dentro do contexto da ELTMF que desenvolvem epilepsia após um período de observação.

O seguimento desses indivíduos pode fornecer pistas sobre a evolução da EH que pode ocorrer independentemente da frequência de crises.

Esse cenário também nos permite avaliar a evolução da EH independentemente da frequência e ocorrência de crises e na ausência de influências medicamentosas.

Não há nenhum estudo prospectivo sobre a evolução natural da ELTMF. Este estudo será fundamental para a melhor compreensão da história natural e dos mecanismos fisiopatológicos da ELTMF.

Objetivos

OBJETIVO

Este trabalho teve como objetivo:

1. Descrever a história natural da ELTMF.
2. Definir quais fatores influenciam nas diferentes evoluções clínicas?
3. Investigar a relação entre a AH e a ELTMF:
    a. Avaliar se há progressão de atrofia hipocampal.
    b. Avaliar se a atrofia hipocampal seria um fator causal da ELTMF (fator único ou um cofator?). E se considerarmos como um cofator quais seriam os outros fatores associados à gênese da ELTMF?
4. Comparar o grau de atrofia de substância cinzenta nos grupos esporádicos ou com histórico familiar de qualquer tipo de epilepsia.

Materiais e Métodos

MATERIAIS E MÉTODOS

Para a realização deste trabalho localizamos e reavaliamos controles sadios e membros pertencentes a famílias com pelo menos dois indivíduos afetados com ELTM, que já haviam sido descritos por nosso grupo em estudo prévio (11, 12). Foram acrescentadas três famílias adicionais que não haviam sido descritas no artigo inicial, mas que foram avaliadas na mesma época. Os dados coletados entre 1997-2002 foram considerados como linha de base para este estudo prospectivo.

Os membros afetados foram localizados nos ambulatórios de Epilepsia do Hospital das Clínicas da UNICAMP ou através de busca pela internet. Através do probando, conseguimos contato com os outros membros da família que foram convidados a retornar para participação neste novo estudo.

Todos os indivíduos contatados assinaram termo de consentimento livre e esclarecido (apêndice 1). Foi realizada uma avaliação clínica com entrevista direcionada e preenchimento do protocolo padrão (apêndice 2). Quando possível, foram adquiridas novas imagens de RM, para comparação com as imagens iniciais.

1. Questões éticas

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP e ofereceu riscos mínimos aos indivíduos avaliados.

Os participantes foram devidamente esclarecidos quanto aos objetivos da pesquisa, quanto à segurança e riscos dos procedimentos realizados e quanto ao sigilo da informação médica. Todos assinaram o termo de consentimento livre e esclarecido específico para tal estudo (apêndice 1).

2. Critérios de Inclusão

Foram incluídos familiares (sintomáticos e assintomáticos) pertencentes às famílias já em seguimento desde 1997.

Em termos práticos, a ELTMF foi definida como famílias com pelo menos dois indivíduos afetados (parentes em primeiro ou segundo grau) com história de crises parciais recorrentes semiologicamente sugestivas de crises de lobo temporal mesial, na ausência de outros tipos de Síndromes Epilépticas na família.

As crises e síndromes epilépticas foram definidas de acordo com a classificação da ILAE. O critério clínico utilizado para definir a ELTM foi a presença de CPS e/ou CPC, com características compatíveis com origem no lobo temporal mesial.

Descargas epileptiformes na região temporal médio-antero-basal e/ou presença de ondas lentas focais na região temporal foram considerados como critérios eletroencefalográficos para ELTM. A presença de EEG normal não excluiu o diagnóstico de ELTM.

3. Critérios de Exclusão

Na seleção inicial foram excluídas as famílias que apresentavam:

- apenas um indivíduo classificado como ELT, independentemente do número de outros familiares com história de crises. (ex. Quando todos os indivíduos possivelmente afetados não estavam disponíveis para avaliação clínica);

- dois indivíduos com diagnóstico clínico de ELTM, porém com exame de EEG e/ou RM sugerindo outra síndrome epiléptica;

- parentes em terceiro ou mais graus com outros tipos de crise;

- suspeita de epilepsia parcial extra-temporal em algum familiar próximo afetado.

No seguimento clínico, foram excluídas famílias em que não foi possível reavaliar pelo menos dois probandos, seja por perda de seguimento, seja por não desejarem mais participar do estudo.

4. Características clínicas e neurofisiológicas

Utilizamos um formulário estruturado contendo informações sobre história familiar e idade de início e frequência das crises (iniciais e atuais), tempo de evolução da epilepsia, antecedentes de IPIs, características clínicas das crises e resposta a drogas antiepilépticas.

Os indivíduos foram divididos em:

1) Afetados: aqueles que preenchiam critérios para ELTM.

2) Não classificáveis: indivíduos pertencentes a famílias com dois indivíduos com diagnóstico de ELTM, que apresentavam história de crises parciais ou generalizadas, mas que não preenchiam critérios para ELTM. Foram incluídos neste grupo pacientes com história de crises febris na infância, crise única ou CTCG sem início parcial identificável por história clínica ou EEG.

3) Assintomáticos: parentes de primeiro ou segundo grau de famílias com ELTMF.

4.1. Estimativa da frequência de crises

A estimativa da frequência das crises foi baseada em calendários de crises e informações obtidas diretamente com os pacientes e familiares, assim como através da revisão de prontuários. Pacientes que preenchiam critérios para ELTM (afetados) foram divididos em três grupos de acordo com a frequência de crises:

1) Remissão: livres de crises pelos últimos dois anos.

2) Benignos: apresentavam menos de 6 CPC por ano e não mais que 2 CTCG por ano.

3) Refratários: 6 ou mais CPC por ano e/ou 2 ou mais CTCG por ano.

O número de crises que definiu cada um dos grupos acima descritos foi determinado de forma arbitrária.

Após a segunda avaliação, os pacientes foram reclassificados de acordo com sua evolução clínica e reagrupados em:

1) Evolução favorável: pacientes que permaneceram ou tornaram-se benignos ou em remissão antes da última avaliação clínica.

2) Evolução desfavorável: pacientes que permaneceram ou tornaram-se refratários durante o seguimento clínico.

4.2. Avaliação dos fatores preditivos

As seguintes variáveis clínicas foram analisadas e correlacionadas com as diferentes evoluções clínicas:

1) Uso de medicação anti-epiléptica na primeira avaliação

2) Presença de alterações epileptiformes no EEG

3) Ocorrência de CTCG em algum momento da vida

4) Antecedente pessoal de IPIs na infância. Foram considerados IPIs a ocorrência de CFs, TCE com perda de consciência, *status epilepticus*, insultos perinatais e infecções de sistema nervoso central.

5) História de possíveis IPIs ocorridos durante a vida adulta (*second hit*)

6) Presença ou ausência de sinais de AH na RM.

4.3. Alterações no eletroencefalograma

A investigação eletroencefalográfica consistiu em uma série de EEGs intercríticos (ambulatóriais) adquiridos em aparelho digital de 32 canais e sistema 10-20 de colocação de eletrodos.

Dos pacientes com crises refratárias, dez realizaram monitorização por video-EEG.

4.4. Classificação quanto a resposta ao tratamento cirúrgico

Os pacientes que foram submetidos à cirurgia de epilepsia foram classificados de acordo com a classificação pós-operatória de Engel.

I. Livre de crises incapacitantes:

IA. Completamente livre de crises desde a cirurgia;

IB. Presença de CPS desde a cirurgia;

IC. Algumas crises incapacitantes após a cirurgia, mas totalmente livre de crises nos últimos dois anos;

ID. Crise convulsiva generalizada decorrente de abstinência de DAE.

II. Crises incapacitantes raras ("quase totalmente livre de crises"):

IIA. Inicialmente livre de crises, mas atualmente com crises raras;

IIB. Crises incapacitantes raras desde a cirurgia;

IIC. Crises incapacitantes desde a cirurgia, mas que se tornaram raras durante o período mínimo de dois anos;

IID. Somente crises noturnas.

III. Melhora (crises, funções cognitivas, qualidade de vida):

IIIA. Redução das crises;

IIIB. Períodos prolongados sem crises até maiores do que a metade do tempo de seguimento, mas não inferiores há dois anos.

IV. Sem melhora:

IVA. Redução significativa das crises;

IVB. Nenhuma mudança;

IVC. Piora das crises.

5. Neuroimagem

Avaliamos o hipocampo dos familiares sintomáticos e assintomáticos por análise visual e análise quantitativa da RM, utilizando diferentes técnicas descritas a seguir. As análises foram realizadas de forma cega, ou seja, sem informações clínicas ou eletroencefalográficas.

Através da comparação com os resultados da avaliação anterior pretendemos:

1. Avaliar a progressão da AH e de estruturas extra-hipocampais.

2. Correlacionar refratariedade com progressão de atrofia.

3. Observar se pacientes com alterações hipocampais assintomáticos evoluíram com crises.

4. Observar se pacientes sem crise com ressonância inicialmente normal desenvolveram alterações no hipocampo.

5.1. Aquisição e análise de RM

As imagens de RM foram obtidas em um sistema de RM de 2 Tesla (Elscint Prestige, Haifa, Israel) com aquisições nos planos coronal, sagital e axial, além de uma aquisição 3D (volumétrica) que permite reconstrução *a posteriori* das imagens em qualquer plano ou inclinação.

Os parâmetros de imagem para as diferentes aquisições foram:

1. Imagens sagitais T1 ponderadas *spin echo* (espessura de 6 mm, ângulo de excitação de 180^{o}, TR= 430, TE= 12, matriz de 200x350, FOV= 25x25 cm). Essas imagens foram utilizadas para orientar o plano de aquisição das demais imagens.

2. Imagens no plano coronal oblíquo, obtidas em um plano perpendicular ao eixo longo da formação hipocampal.

a) T2 ponderadas e densidade de prótons *fast spin echo* (espessura de 3 mm; ângulo de excitação de 120^{o}; TR= 5800; TE= 129; matriz de 252x320; FOV= 18x18 cm); ou imagem ponderada em T2 e densidade de prótons "fast spin echo"; 3mm de espessura; ângulo de excitação de 160°; TR, 4600; TE, 108/18; matriz, 256X256; FOV, 22X22 cm;.

b) *Inversion recovery* ponderadas em T1 (espessura de 3 mm; ângulo de excitação de 200^{o}; TR IR 2800; TE= 14; TI= 840; matriz de 130x256; FOV= 16x18 cm).

3. Imagens no plano axial: paralelas ao eixo longo do hipocampo:

a) imagem ponderada em T1 e gradiente eco; 3mm de espessura; ângulo de excitação de 70°; TR 200; TE, 5.27; matriz, 230X230; e FOV, 22X22 cm;

b) FLAIR (*fluid attenuated inversion recovery*) 5 mm de espessura; ângulo de excitação de 110°; TR 10099; TE, 90; matriz, 250x250; e FOV, 24X24 cm;

4. Imagem volumétrica ponderadas em T1 gradiente eco com voxels isotrópicos de 1mm, adquiridos no plano sagital (1mm de espessura; ângulo de excitação de 35°; TR, 22; TE, 9; matriz, 256x220; e FOV, 25x22cm); ou com 1,5x1x1mm de espessura transformados posteriormente em voxels isotrópicos.

5.1.1. Análise Visual

Na análise visual, observamos de forma sistemática a presença de lesões estruturais e suas características. A análise das imagens foi feita sem o conhecimento da classificação clínica dos pacientes.

Nessa análise, observamos a presença de assimetria, e de alterações de sinal, forma, tamanho e orientação espacial do hipocampo. A reconstrução multiplanar foi utilizada quando a análise convencional das imagens de RM não mostrava alterações.

Todas as alterações observadas na RM foram classificadas de acordo com os seguintes parâmetros:

1) Tamanho (normal, atrofia leve, moderada e grave)

2) Forma (normal ou alterada)

3) Eixo (normal ou rodado) (Figura 3)

4) Sinal (normal ou alterado)

5) Assimetria (normal, AH unilateral ou bilateral

Análise visual do hipocampo

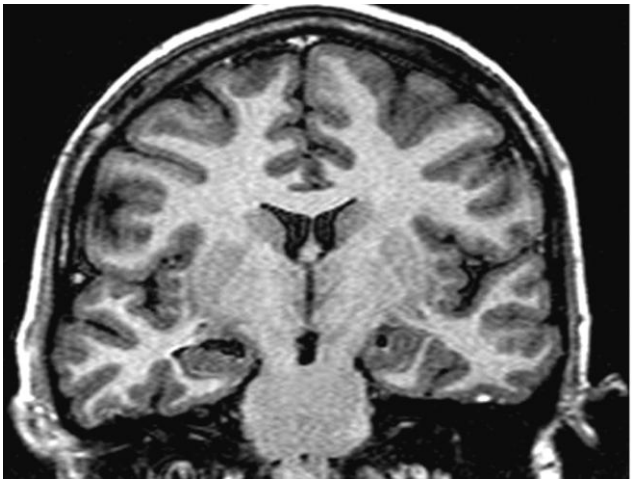

Figura 2. Exemplo de alteração do eixo do hipocampo à esquerda

Para comparação com dados clínicos, os pacientes foram divididos em dois subgrupos de acordo com o grau de AH pela análise visual (considerando sempre o lado mais afetado):

1) Normal: hipocampos normais ou com alterações discretas

2) Hipocampo atrófico: atrofia moderada a grave.

5.1.2. Volumetria manual

Para a realização dos estudos volumétricos manuais utilizamos o aplicativo semiautomático Scion Image Software que permite o traçado manual das estruturas temporais mesiais. Foram utilizadas os cortes coronais de 3mm T1-"*inversion recovery*"

(T1-IR) (ângulo de excitação de 200°; TR = 2800, TE = 14, TI = 840, matriz 130 × 256, FOV = 16 cm × 18 cm). Os parâmetros anatômicos utilizados para o estudo volumétrico são descritos em protocolos publicados previamente (57-59). Os volumes obtidos foram normalizados para o volume cerebral total permitindo uma comparação direta entre indivíduos com perímetros cefálicos diferentes.

Consideramos presença de AH quando o volume total e/ou o índice de assimetria eram inferiores a dois desvios-padrão abaixo da média do grupo controle (Z-score < ou = a -2).

5.1.3. Morfometria Baseada em voxel

Utilizamos também o método MBV. Esse método permite a comparação entre imagens utilizando a segmentação automática, que tem como vantagens a redução do tempo de interação entre usuário e computador e a redução do viés do examinador. A MBV é realizada através da determinação da concentração de tecidos cerebrais como substância cinzenta, substância branca e líquor.

Como objetivo de viabilizar a comparação, as imagens de RM são previamente processadas seguindo os seguintes passos:

- Normalização: as imagens são redimensionadas para um espaço padrão, tendo como base um 'cérebro padrão' adquirido de indivíduos controles normais de diversas faixas etárias. Este passo reduz a variação anatômica entre indivíduos.

- Segmentação: a estrutura alvo é automaticamente segmentada.

- Modulação: realizada principalmente na presença de áreas importantes de atrofia. Este procedimento preserva as áreas atróficas que eventualmente tenham sido distorcidas pela normalização.

- Suavização: Através da aplicação de um filtro a imagem é suavizada. A imagem suavizada reduz a variação interindividual dos giros cerebrais.

Após o processamento, este método permite a comparação entre grupos de imagens utilizando a análise estatística apropriada. O programa realiza a comparação voxel por voxel entre grupos. A comparação avalia a probabilidade de cada voxel ser substância cinzenta, substância branca ou líquor. O resultado das múltiplas comparações é o mapa paramétrico estatístico. Em seguida, o resultado geralmente é corrigido para a distribuição normalizada, indicando o número de desvios padrão entre as amostras (55, 60).

6. Análise Estatística

Os dados clínicos obtidos foram tabulados. O teste de *Kolmogorov-Smirnov* foi aplicado para análise do tipo de distribuição das variáveis numéricas. As variáveis paramétricas com distribuição normal foram analisadas com o teste *T* de Student, teste t pareado ou ANOVA com Teste post hoc de Tukey.

Para análise das variáveis categóricas foi utilizado o teste exato de Fisher.

As correlações dos resultados da análise, qualitativa e quantitativa da RM com EEG e outras variáveis foram analisadas por um modelo de regressão logística multivariada (*backward stepwise logistic regression analysis*).

Resultados

RESULTADOS

1. Descrição da casuística

Realizamos um estudo longitudinal com 103 indivíduos pertencentes a 17 famílias. Das 22 famílias descritas no artigo inicial reavaliamos 14 e acrescentamos três famílias. Apesar de não terem sido incluídas no artigo de 2002, a primeira avaliação dessas famílias foi realizada no mesmo período (2002). Os dados clínicos e os heredogramas estão descritos nos anexos 3 e 4.

Dos 103 indivíduos reavaliados, 53 foram classificados na primeira avaliação como afetados, 18 como não classificáveis e 32 como assintomáticos. Os pacientes afetados foram subdivididos em três grupos: 19 pacientes foram inicialmente considerados em remissão (7 homens), 17 benignos (6 homens) e 17 refratários (6 homens).

1.1. Descrição das variáveis clínicas na primeira avaliação (assintomáticos, não classificáveis e afetados)

As diferenças entre as variáveis clínicas observadas nos três grupos analisados estão descritas na tabela 1.

Tabela 1. Variáveis clínicas observadas				
	Assintomáticos (n=32)	Não classificáveis (n=18)	Afetados (n=53)	*p*
Idade na RM1 (anos)	33,78 ± 14,44 (9 a 73)	29,44 ± 15,79 (5 a 58)	34,03 ± 13,04 (8 a 66)	*p*=0,466 (ANOVA)
Tempo entre as avaliações (meses)	81,19 ± 13,48 (63,8 a 108,72)	94,29 ± 19,69 (63,8 a 108,72)	97,28 ±23,2 (31,1 a 155,1)	*p*=0,002 (ANOVA)
Idade de inicio das crises	NA	8,27 ± 7,17 meses (11 meses a 30 anos, 2 com início na infância)	7,81 ± 6,34 anos (8 meses a 27 anos)	*p*=0,816 (teste *t*)
Sexo (M/F)	17/15	7/11	24/29	*p*=0,602 (X^2)
Dados descritos como média ± desvios-padrão (valor mínimo a valor máximo); RM1, primeira ressonância magnética; M, masculino; F, Feminino; NA, não se aplica; X^2, qui-quadrado.				

Os grupos avaliados foram semelhantes em relação à idade na primeira avaliação, a idade de início das crises e ao sexo. Houve diferença entre o tempo de seguimento dos três grupos (*p*= 0.002, ANOVA), sendo que nos assintomáticos a média de tempo entre as duas avaliações foi inferior a do grupo afetado (*p*=0,002; Post Hoc – teste de Tukey).

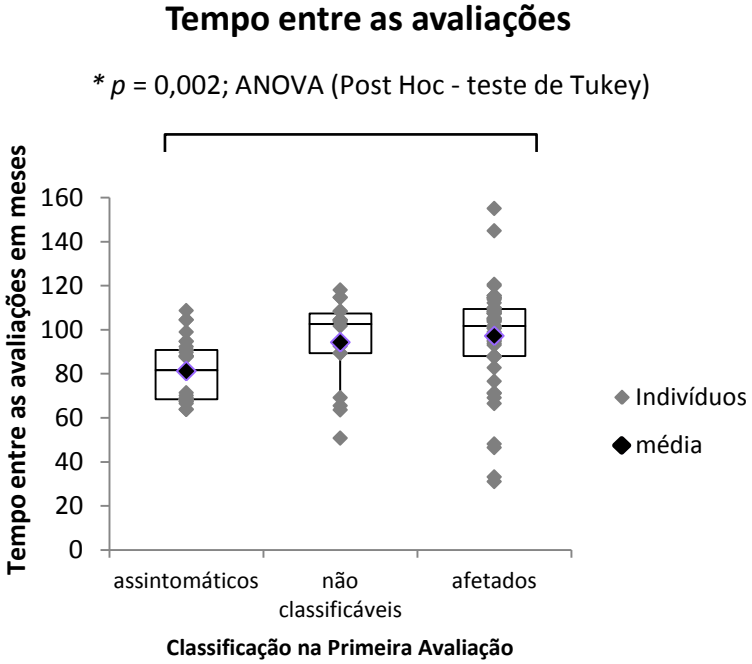

Figura 3. Gráfico mostrando a distribuição do tempo de seguimento clínico dos diferentes subgrupos.

1.2. Comparação entre assintomáticos, remissão, benignos, refratários e não classificáveis.

Quando subdividimos o grupo de pacientes afetados em remissão, benignos e refratários e comparamos o tempo de seguimento entre os cinco grupos (figura 4) a diferença permaneceu (p=0,013, ANOVA), sendo que tempo de seguimento do grupo assintomático foi inferior ao do grupo benigno (p=0,025; Post Hoc – teste de Tukey). Não houve diferença entre a média de idade dos cinco grupos. (p= 0.220, ANOVA, Post Hoc – teste de Tukey).

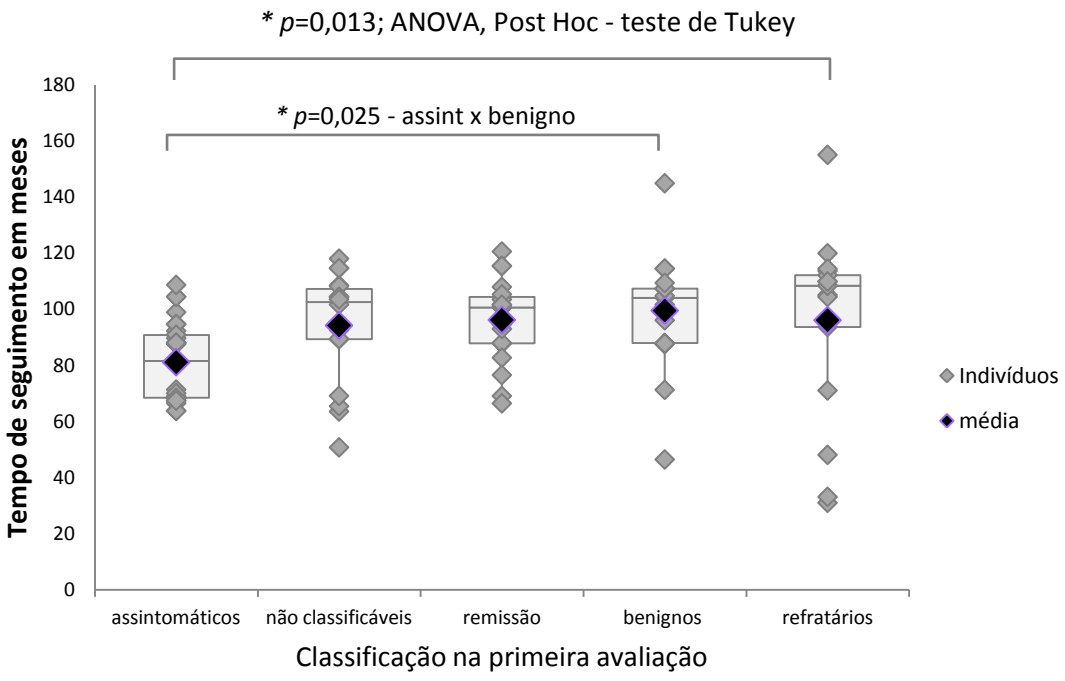

Figura 4. Gráfico mostrando a distribuição do tempo de seguimento clínico dos diferentes subgrupos.

1.3. Comparação dos subgrupos de pacientes com ELTM (remissão, benignos e refratários).

Em relação à idade de inicio da epilepsia o grupo de pacientes refratários teve idade de início das crises inferior ao grupo benigno e remissão. Na análise estatística houve diferença entre os três grupos (p= 0.025, ANOVA), sendo que a diferença foi entre o grupo de refratários e benignos (p=0,019, Post Hoc – teste de Tukey). Não houve diferença entre os grupos refratários versus remissão e benigno versus remissão. (figura 5)

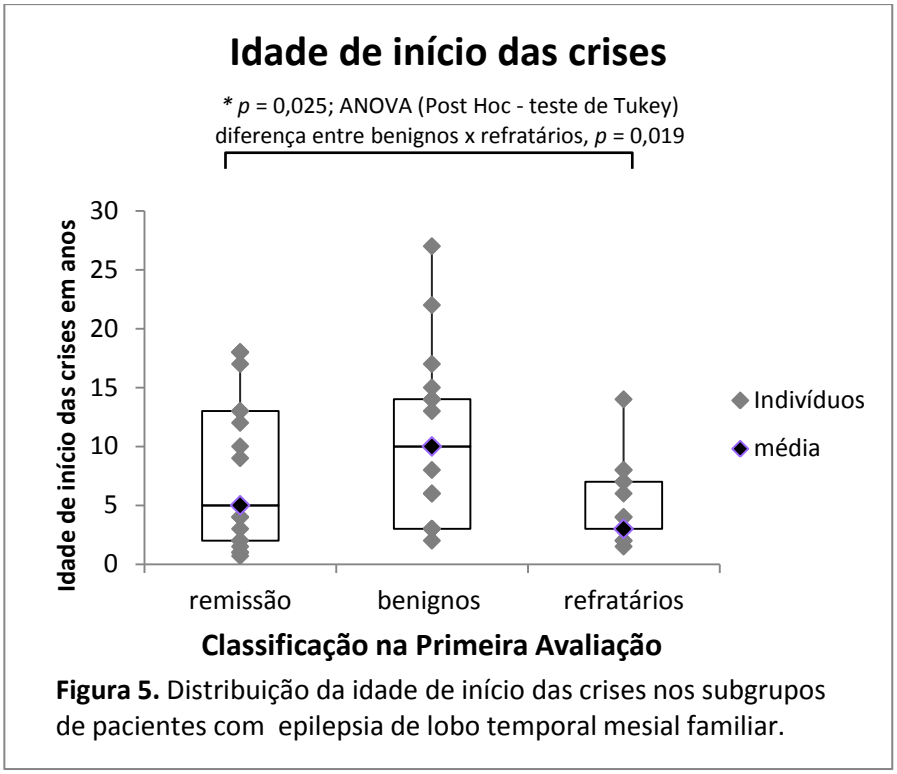

Figura 5. Distribuição da idade de início das crises nos subgrupos de pacientes com epilepsia de lobo temporal mesial familiar.

A comparação da distribuição das diferentes variáveis clínicas na primeira avaliação encontra-se descrita na tabela 2.

Tabela 2. Comparação das variáveis clínicas nos subgrupos de pacientes afetados na primeira avaliação

Fatores	Remissão (n=19)	Benignos (n=17)	Refratários (n=17)	*p* (Fisher)
DAE 1ª avaliação *	6 (33,3%)*	13 (76,5%)	17 (100%)	< 0,001
AE no EEG *	1 (10%)*	9 (30,8%)*	17 (100%)	< 0,001
CTCG	13 (68,4%)	14 (82,4%)	17 (100%)	0,037
IPIs	4 (21,1%)	6 (35,3%)	6 (35,3%)	0,602
Second hit	2 (10,5%)	6 (35,5%)	7 (41,2%)	0,087

*alguns pacientes não apresentavam a informação disponível, nestes casos estes pacientes foram excluídos do cálculo de proporção e estatística. DAE, droga antiepiléptica; AE, atividade epileptiforme; EEG, eletroencefalograma; CTCG, crise tônico-clônica generalizada; IPI, insulto precipitante inicial.

Na análise dos dados clínicos obtidos na primeira avaliação observamos que o grupo de pacientes refratários fazia mais uso de medicação anti-epiléptica, apresentava mais atividade epileptiforme no EEG e apresentava mais antecedente de CTCG que os outros grupos. (Figura 6)

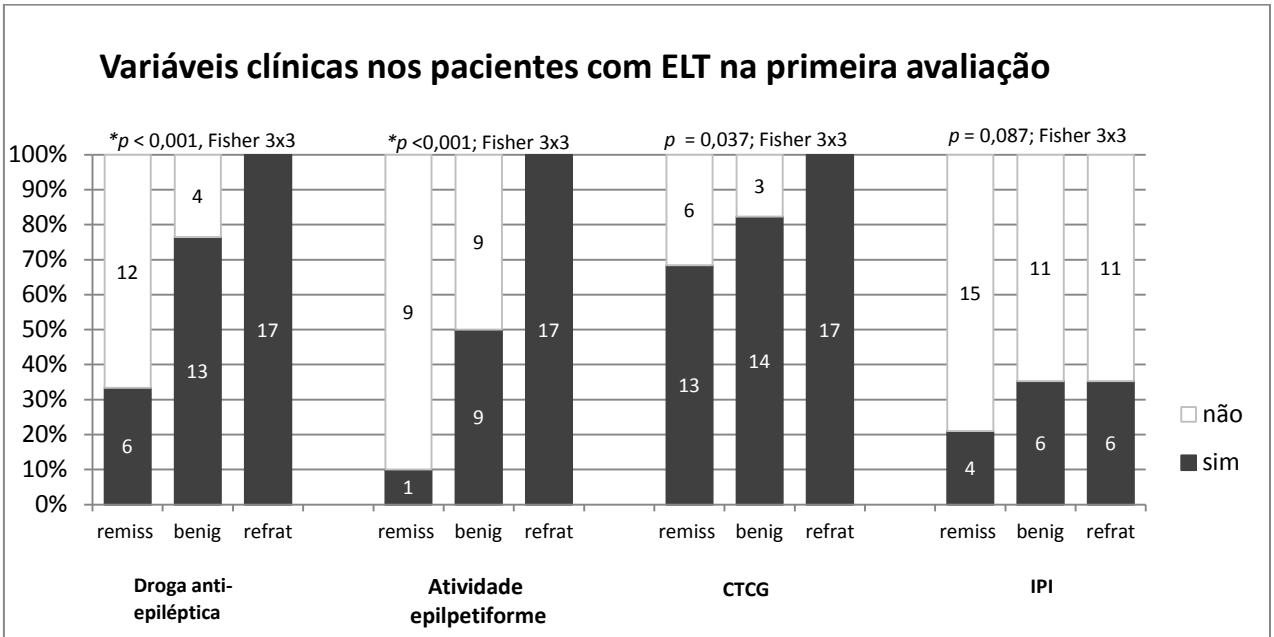

Figura 6. Distribuição das diferentes variáveis clínicas na primeira avaliação.
Legenda: ELT, epilepsia de lobo temporal; remiss, remissão; benig, benigno; refrat, refratário; CTCG, crise tônico-clônica generalizada; IPI, insulto precipitante inicial.

2. Distribuição de acordo com as diferentes evoluções clínicas

A distribuição das diferentes evoluções clínicas no seguimento prospectivo é mostrada na figura 2. Dos 32 pacientes assintomáticos avaliados quatro (12,5%) evoluíram com crises e passaram a preencher critérios para ELTM. Dos 18 pacientes que inicialmente não preenchiam critérios para ELTM quatro (22,2%) fecharam critérios para ELTM.

Após o seguimento clínico de em média sete anos, a maioria dos pacientes afetados permaneceu no mesmo status clínico. Dos pacientes inicialmente classificados como benignos 23,5 % entraram em remissão e 17.6 % tornaram-se refratários. No grupo inicialmente em remissão quatro (21.1%) tornaram-se benignos. Todos os pacientes refratários permaneceram refratários ou foram submetidos à cirurgia de epilepsia. (figura 7)

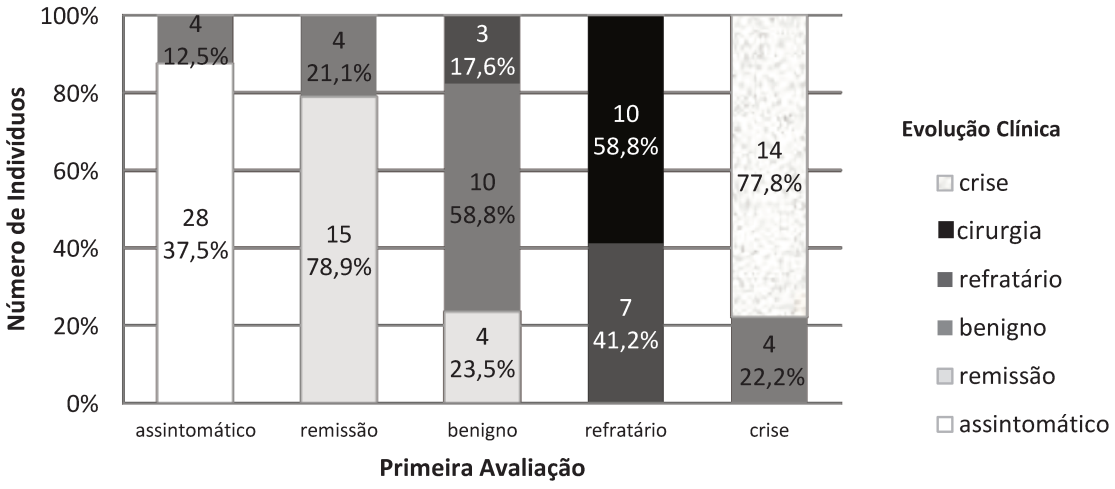

Figura 7. Gráfico mostrando a distribuição da classificação de acordo com a frequência de crises nos dois tempos do estudo (avaliação inicial e evolução clínica). Crise=grupo com crises não classificadas.

2.1. Análise das variáveis correlacionadas com evolução clínica

De acordo com a evolução clínica os pacientes foram reclassificados em evolução clínica favorável (n=10; 62,2%), desfavorável (n=33; 18,9%) e cirúrgicos (n=10; 18,9%).

A comparação da distribuição das diferentes variáveis clínicas entre os grupos com evolução clínica favorável e desfavorável encontra-se descrita na figura 8.

Não houve diferença entre os grupos com evolução clínica favorável ou desfavorável em relação ao do uso de DAE na avaliação inicial e ocorrência de CTCG em algum momento da vida. Houve diferença entre os grupos com evolução clínica favorável ou desfavorável em relação à presença de atividade epileptiforme no EEG (p=0,0174; teste exato de Fisher) e presença de alterações de volume hipocampal na RM (p=0,0192, teste exato de Fisher). Não observamos diferença em relação ao antecedente de IPIs, apesar de observarmos uma tendência (p=0,0549; teste exato de Fisher).

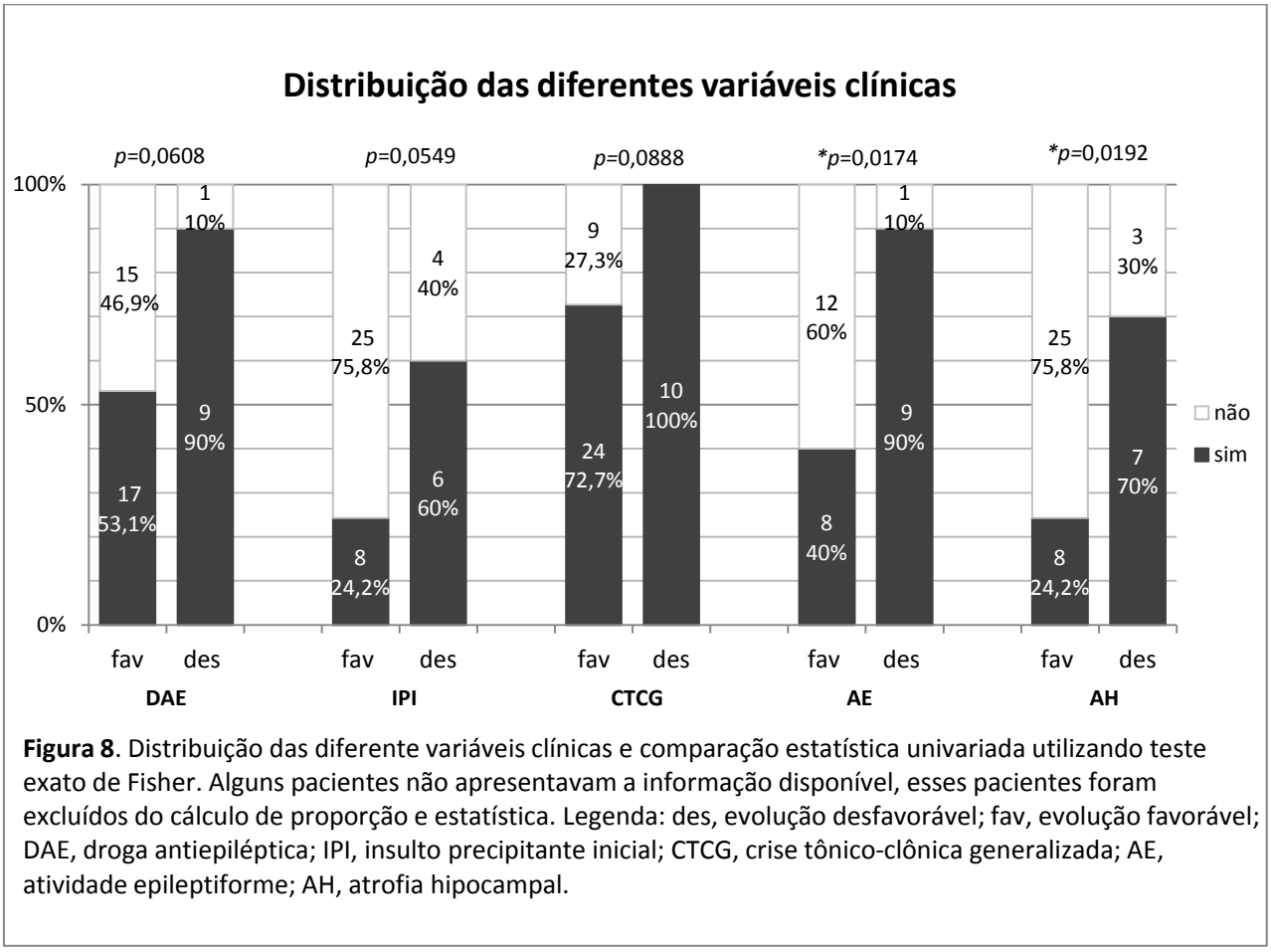

Figura 8. Distribuição das diferente variáveis clínicas e comparação estatística univariada utilizando teste exato de Fisher. Alguns pacientes não apresentavam a informação disponível, esses pacientes foram excluídos do cálculo de proporção e estatística. Legenda: des, evolução desfavorável; fav, evolução favorável; DAE, droga antiepiléptica; IPI, insulto precipitante inicial; CTCG, crise tônico-clônica generalizada; AE, atividade epileptiforme; AH, atrofia hipocampal.

A análise por regressão logística multivariada comparando as diferentes evoluções (favorável e desfavorável) incluindo todas as variáveis clínicas foi significativa (p=0.008), e a regressão logística (*backward stepwise logistic regression analysis*) demonstrou que o melhor modelo incluiu a AH e AE no EEG (p=0.001) para o prognóstico desfavorável.

3. Avaliação visual das imagens de RM

Foi realizada a análise visual de pelo menos uma das imagens de RM dos pacientes.

A distribuição da presença de sinais de AH no hipocampo mais afetado está descrita na tabela 3. Considerando os resultados da avaliação visual da RM agrupados em "sem atrofia" + "atrofia leve" versus "atrofia moderada" + "grave" houve diferença significativa, com maior freqüência de atrofia moderada-grave no grupo refratário (Teste exato de Fisher, p<0,001).

Tabela 3. Pacientes distribuídos de acordo com a presença de alterações do volume do hipocampo na análise visual.				
	Sinais de atrofia no hipocampo mais afetado			
	Sem atrofia	**leve**	**moderada**	**grave**
Assint	20 (62,5%)	11 (34,4%)	0	1 (3,1%)
Não classif	14 (77,8%)	2 (11,1%)	1 (5,6%)	1 (5,6%)
Remissão	7 (36,8%)	7 (36,8%)	2 (10,5%)	3 (15,8%)
Benigno	9 (52,9%)	4 (23,5%)	3 (17,6%)	1 (5,9%)
Refratários	0	1 (5,9%)	0	16 (94,1%)

Assint, assintomático; não classif, não classificável; normal, ausência de sinais de atrofia nos hipocampos; leve, hipocampo mais afetado com atrofia leve; moderada, hipocampo mais afetado com atrofia moderada; grave, hipocampo mais afetado com atrofia grave.

Em relação ao lado com sinais AH observamos a distribuição descrita na tabela 4.

Tabela 4. Tabela mostrando o lado do hipocampo com alterações de volume na análise visual			
	Lado afetado		
	Direito	**Esquerdo**	**Bilateral**
Assint	0	7 (58,3%)	5 (41,7%)
Não classif	2 (50%)	2 (50%)	0
Remissão	2 (16,7%)	5 (41,7%)	5 (41,7%)
Benigno	3 (37,5%)	1 (12,5%)	4 (50%)
Refratários	5 (29,4%)	5 (29,4%)	7 (41,2%)

Assint, assintomático; não classif, não classificável.

A distribuição das outras alterações encontradas no hipocampo na análise visual é demonstrada na tabela 5.

Tabela 5. Pacientes distribuídos de acordo com a presença de alterações do eixo, forma e sinal do hipocampo na análise visual.				
Grupo	**Sem atrofia**	**Forma/eixo**	**Sinal**	**Sinal/forma/eixo**
Assint	18 (56,3%)	12 (37,5%)	1 (3,1%)	1(3,1%)
Não classif	10 (55,5%)	3 (16,7%)	0	5 (27,8%)
Remissão	8 (42,1%)	4 (21,1%)	1 (5,2%)	6 (31,6%)
Benigno	8 (47,1%)	5 (29,4%)	1 (5,9%)	3 (17,6%)
Refratários	1 (5,9%)	0	0	16 (94,1%)

Assint, assintomático; não classif, não classificável; forma/eixo, alteração de forma e/ou eixo; sinal, alteração de sinal; sinal/forma/eixo, alteração de forma, eixo e sinal do hipocampo.

Pela análise visual 19 pacientes assintomáticos apresentavam alterações hipocampais. (cinco indivíduos apresentavam alteração isolada de volume e 14 apresentavam alteração de sinal, eixo e/ou forma associada à alteração leve de volume (n=7) ou não (n=7)).

4. Avaliação de progressão de dano

Como segunda parte deste trabalho, resolvemos estender este estudo e comparar a progressão de AH de pacientes com e sem histórico familiar de ELTM.

Para isso realizamos um estudo com 35 pacientes com ELTMF e 33 com ELTM esporádica. As imagens de RM adquiridas em dois tempos distintos foram analisadas de forma cega, com o objetivo de comparar o volume do hipocampo na primeira

imagem com o volume aferido na segunda imagem. Para isso realizamos a volumetria manual dos hipocampos utilizando o programa *Scion Image*. Os volumes também forma comparados com controles para definir a presença de AH (foi considerada AH quando o volume do hipocampo era inferior a dois desvios-padrão).

O intervalo médio entre as duas imagens foi de 90 meses para os pacientes com quadro familiar e de 45 meses para os esporádicos. Em relação à frequência de crises o grupo de familiares foi composto por 25 pacientes classificados como benignos e 10 refratários. Já o grupo esporádico foi composto por quatro pacientes com quadro benigno e 29 com quadro refratário.

A análise de volumetria do grupo com ELTMF mostrou presença de AH em 20 pacientes na RM1 e 23 na RM2. A análise de grupo mostrou diferença significativa entre o volume do hipocampo dos controles em relação aos afetados.

Houve uma significativa redução de volume entre as duas RMs. (ELTMF hipocampo direto: $p<0,001$ e hipocampo esquerdo, $p<0,001$; teste *t* pareado). Tal redução persistiu mesmo quando subdividimos os familiares em benignos e refratários. (ELTMF benigna: hipocampo direto: $p = 0,001$ e hipocampo esquerdo, $p< 0,001$; ELTMF refratária hipocampo direito, $p = 0,022$ e hipocampo esquerdo, $p < 0.010$; teste *t* pareado).

A análise de volumetria do grupo esporádico mostrou presença de AH em 27 pacientes na RM1 e 29 na RM2. A análise de grupo também mostrou diferença significativa entre o volume do hipocampo dos controles em relação aos afetados. O teste *t* pareado comparando volume hipocampal nas duas RMs também mostrou redução significativa do hipocampo direito ($p=0,009$) e do esquerdo ($p=0,0025$) com o passar do tempo. Como o n do grupo de esporádicos benignos era muito baixo não foi possível

realizar a análise estatística adequada para comparação dos dois grupos (benignos x refratários).

Apesar do tempo de seguimento do grupo familiar ter sido o dobro do grupo esporádico, não houve diferença estatística entre o grau de progressão de atrofia entre os dois grupos. (hipocampo D, p=0.886; hipocampo esquerdo, p=0.598; teste t), indicando que a progressão no grupo familiar deva ser mais lenta que no grupo de esporádicos.

Maiores detalhes desta parte da tese estão incluídos no artigo em anexo. (apêndice 5)

5. Avaliação com MVB

Como terceira parte deste estudo, nós tentamos ampliar o conceito de influência genética sobre a ELTM. Para isso, optamos por estudar um espectro mais amplo de influência genética, comparando pacientes sem nenhuma história genética com pacientes com diversos graus de influência genética.

O objetivo deste estudo teve como base o fato de acreditarmos que a doença tem um *continuum* biológico com duas extremidades. Em um extremo teríamos pacientes "puramente genéticos". Neste extremo o grupo que mais se aproximaria desta situação, clinicamente improvável, seriam os pacientes com ELTMF. No outro extremo teríamos pacientes com nenhuma ou quase nenhuma influência genética (considerados como influência quase que exclusivamente ambiental). Neste caso, pacientes chamados

esporádicos. Entre estes dois extremos ficariam os pacientes com história familiar sem necessariamente apresentarem ELTMF.

A análise dos casos refratários englobando todo espectro deste *continuum* biológico foi realizada na tentativa de investigar os danos neuronais e influência dos dados clínicos nos diferentes espectros deste *continuum*.

Neste estudo analisamos 69 pacientes com ELTM unilateral submetidos à cirurgia de epilepsia e 69 controles. Destes 29 (média de idade 35,8 ± 10,4 anos) não apresentavam história familiar de epilepsia e 40 (média de idade 32,8 ± 10 anos) apresentavam algum membro na família (parente de primeiro ou segundo grau) com o diagnóstico de epilepsia (não necessariamente ELTM).

Realizamos a análise das imagens de RM adquiridas no pré-operatório. Utilizando o método MBV e teste *t* comparamos os dois grupos com controles. Investigamos também as diferenças clínicas e neuropsicológicas entre os dois grupos.

Em relação ao grupo com história familiar, o grupo esporádico apresentou QI inferior p=0,004 e pior desempenho nos testes neuropsicológicos (*Boston Naming Test* (p=0,02) e *delayed recall* (p=0,03)). Além disso, no grupo esporádico o índice de assimetria na volumetria dos hipocampos foi mais acentuado (p=0,04) e o antecedente pessoal de IPI também foi mais frequente.

Em relação à MBV observamos um padrão mais restrito de atrofia de substância cinzenta no grupo com história familiar e um padrão mais bilateral e difuso no grupo esporádico (figura anexa ao paper, apêndice 6). A atrofia de substância branca foi difusa e bilateral em ambos os grupos.

Maiores detalhes desta parte da tese estão incluídos no artigo em anexo. (apêndice 6)

Discussão

DISCUSSÃO

Neste estudo, realizamos uma análise longitudinal da ELTMF baseada em dados clínicos e de neuroimagem, com o objetivo de ampliar o conhecimento sobre a história natural da ELTMF e buscar possíveis fatores preditivos que influenciem nas diferentes evoluções clínicas desta patologia. O aprimoramento do conhecimento atual sobre a história natural da ELTMF não só auxilia no manuseio clínico destes pacientes como também fornece ferramentas para melhor compreendermos a fisiopatologia desta doença.

Em relação à frequência de crises, o estudo prospectivo destas famílias mostrou que na ELTMF pacientes com boa evolução clínica tendem a permanecer nesse mesmo *status* com o passar dos anos (com relativo bom controle de crises ou em remissão). Já os pacientes refratários por um período maior que um ano tendem a permanecer refratários, exceto quando submetidos ao tratamento cirúrgico. Dessa forma, nos casos de refratariedade ou evolução para refratariedade na ELTMF, a cirurgia deve sempre ser considerada.

Alguns poucos pacientes com quadro inicialmente benigno evoluíram para refratariedade. Estes eram possivelmente pacientes que estariam no chamado "período latente" ou que se tornariam refratários como parte de sua evolução clínica natural.

Alguns pacientes assintomáticos (12,5%) com história familiar de ELTMF desenvolveram crises durante o seguimento clínico, enquanto que nenhum dos controles

evoluiu com crises. A ocorrência de crises isoladas ou não classificáveis não determinou necessariamente o desenvolvimento de ELTM.

Apesar da existência de casos refratários, os dados mostrados neste estudo confirmam o caráter mais benigno da ELTMF (42). Eles reforçam a existência de ELTM com evolução benigna, que raramente é descrita na literatura (6). Tal fato talvez se deva não só ao predomínio de estudos de séries cirúrgicas, mas também ao fato de que pacientes com bom controle de crise não necessitam de tratamento especializado e acabam não sendo descritos na literatura.

A persistência do bom controle de crises com o passar dos anos mostra que pacientes inicialmente classificados como benignos não apresentaram necessariamente uma evolução desfavorável num seguimento em longo prazo e fala contra a hipótese de que esses pacientes estivessem, por exemplo, em um período latente na primeira avaliação. Em outras palavras, o período latente seguido de refratariedade descrito nas series cirúrgicas parece não ser regra na história natural da ELTMF.

Além disso, o seguimento clínico prospectivo de uma coorte de famílias com ELTMF permitiu a observação de pacientes com ELTM que apresentavam variadas frequências de crises, abrangendo um espectro que varia desde indivíduos com crise única, até aqueles com quadro refratário, incluindo até mesmo indivíduos assintomáticos. Desta forma, podemos dizer que, ao contrário do que ocorre nos estudos de séries cirúrgicas, a análise das famílias aproxima-se muito mais da realidade, representando de certa forma um microcosmo da população geral. Neste contexto, o seguimento das famílias permite a realização de RM e coleta de dados clínicos em dois tempos. Essa aquisição de informações seria extremamente difícil de ser obtida em um estudo populacional. Não podemos

esquecer, no entanto que, ao contrário do que ocorre na população geral, no estudo das famílias há uma forte predisposição genética que precisa ser lembrada ao extrapolarmos os resultados obtidos para a população geral. De qualquer forma, o fato de alguns indivíduos assintomáticos (12,5%) terem desenvolvido crises durante o período de seguimento prova que esta foi uma boa estratégia.

Em relação aos fatores que influenciaram as diferentes evoluções clínicas, observamos que a presença de AH moderada e grave na RM (p=0,0192) e a presença de alterações epileptiformes no EEG (p=0,0174) foram significativamente mais frequentes nos pacientes com evolução clínica desfavorável. Observamos também uma tendência à maior ocorrência de antecedente pessoal de IPIs no grupo com evolução desfavorável (p=0,0549). A idade de início de crises também foi mais precoce no grupo de pacientes refratários, como observado em alguns estudos prévios. (5)

Em relação à importância do EEG como fator prognóstico de resposta ao tratamento clínico nas epilepsias parciais, estudos prévios demonstram resultados discordantes. Alguns demonstram uma relação entre atividade interictal e evolução desfavorável (61, 62), enquanto em outros essa associação não é significativa (63). Entretanto, a maioria são estudos transversais e não discriminam o tipo de epilepsia parcial, incluindo pacientes com etiologias diversas. O mesmo não acontece com as epilepsias generalizadas, sobretudo a epilepsia ausência na infância, em que o EEG interictal tem boa relação com o controle de crises, ou seja, a presença de atividade epileptiforme interictal está relacionada com a maior probabilidade de ocorrência de crises (64). A presença de AE como fator preditivo em nosso trabalho foi um achado importante, indicando que, pelo

menos no contexto da ELTMF, os EEGs interictais com AE parecem ser preditores de evolução desfavorável.

Em relação aos IPIS, observamos uma tendência (p=0,0549) a considerá-los como fator preditivo de evolução desfavorável. Este é um importante achado, pois mostra que os IPIS podem estar relacionados às diferentes evoluções clínicas. Em outras palavras, a exposição a fatores ambientais também parece influenciar no curso da doença. Esta teoria poderia explicar algumas divergências na literatura em relação à benignidade x heterogeneidade fenotípica observada nas diferentes descrições clínicas de ELTMF (11, 65, 66).

A associação entre ELTM e AH é bem descrita na literatura (18, 22). No entanto, a presença de sinais de AH na RM de pacientes com bom controle clínico ainda não foi investigada de forma prospectiva, especialmente em séries não cirúrgicas. A presença de sinais de alterações hipocampais em pacientes assintomáticos fala a favor da hipótese de que a AH ocorra antes do início das crises e confirma a provável influência genética nessa alteração estrutural. A presença ou ausência de AH não foi um indicador absoluto de refratariedade, já que uma boa proporção de pacientes com AH apresentou bom controle de crises. Esse achado fortalece ainda mais a teoria de que mecanismos geneticamente determinados podem ter papel importante na gênese da AH, pelo menos nos casos familiares.

A influência do grau de atrofia na refratariedade já foi abordada em análise transversal que mostrou maior AH em pacientes com ELTMF com quadro refratário (46). A avaliação longitudinal realizada neste estudo confirma a importância do grau de AH (moderada a grave) na evolução clínica de pacientes com ELTMF, que foi considerado

fator preditivo de evolução clínica desfavorável (p=0,0192). Este achado pode ser um indício de que a AH tenha um caráter progressivo com diversos graus de acometimento. A existência de atrofia influenciaria na gênese da ELTM, porém, por si só, não necessariamente levaria a crises. Cofatores poderiam, por exemplo, acelerar o processo de progressão de atrofia, definindo ou não a ocorrência de crises e sua gravidade.

O achado de progressão de AH no pacientes com ELTM esporádicos e com ELTMF corrobora essa hipótese. As próprias crises parecem ter um papel como catalisadoras de tal progressão. De uma forma mais global poderíamos até mesmo incluir os IPIs nesse raciocínio. Os IPIs atuariam como cofatores que somados ou não a uma influência genética poderiam causar maior lesão hipocampal e acelerar o aparecimento das crises, definindo ou não a presença de ELTM e sua gravidade. Vale a pena lembrar que também existem pacientes com ELTM sem AH que desenvolvem crises; e algumas vezes crises refratárias. Seguindo esse mesmo raciocínio, a AH poderia causar a ELTM, porém não seria condição indispensável. Outros fatores quando somados também poderiam determinar a ocorrência de ELTM por si só.

Em resumo, os dados apresentados corroboram a hipótese de que a ELTM poderia representar o resultado final comum a processos fisiopatológicos completamente distintos, em que a somatória de diversos fatores e cofatores poderia causar e determinar a gravidade da ELTM. Em outras palavras, a influência genética por si só poderia determinar a ocorrência de ELTM, porém, quando agindo de forma isolada, talvez gerasse um quadro clinicamente mais benigno conforme descrito na literatura e demonstrado neste estudo. A adição de novos fatores ao longo da vida poderia determinar o agravamento de uma predisposição, ou seja, quanto mais fatores, maior a probabilidade de desenvolvimento de

um quadro mais grave. Esses fatores poderiam ser, por exemplo, infecções do SNC, a ocorrência de CFs, TCE, problemas perinatais, crises prolongadas e outros fatores que ainda desconhecemos.

O fato de a progressão de atrofia ser mais acentuada em pacientes afetados que no grupo controle, assim como a descrição de casos com atrofia de novo após encefalites ou pós-estado de mal epiléptico fortalecem esta teoria.

Além disso, os resultados obtidos através da comparação de MBV entre pacientes com ELTM esporádica e pacientes com ELTM com qualquer tipo de antecedente familiar para epilepsia são compatíveis com tais hipóteses, já que teoricamente pacientes sem influência genética (esporádicos) necessitariam de maior influência ambiental para desenvolver a ELTM. Nesse caso, teriam provavelmente lesões mais difusas que aqueles com predisposição genética. Em outras palavras, de acordo com esta hipótese quanto maior o componente genético, menor a intensidade necessária de outros danos para gerar ELTM.

Nos grupos de pacientes assintomáticos e não classificáveis o número de pacientes que mudaram de *status* foi muito pequeno para a definição de fatores prognósticos para evolução clínica, porém a proporção de indivíduos nesses dois subgrupos que evoluíram para o diagnóstico de ELTM benigna (12,5% e 22%) no tempo de seguimento deste estudo foi maior do que o esperado para a população geral (incidência acumulada de 1,7%) (67).

O presente estudo apresenta uma análise de casos tanto refratários quanto benignos. O estudo dos casos com evolução clínica favorável é de extrema importância, pois a observação de diferenças clínicas e de neuroimagem entre grupos com diferentes

cursos de doença fortalece a hipótese de que a fisiopatologia da ELTM seja definida por uma somatória de fatores que teriam como produto final a ELTM.

Este é o primeiro estudo a realizar uma análise longitudinal da ELTMF com o objetivo de melhor compreender a história natural da doença. Mostramos que, apesar de a maioria dos pacientes ter permanecido no mesmo *status* clínico durante o período analisado, aqueles que evoluíram para refratariedade foram os que apresentavam sinais mais intensos de EH na RM (alteração de sinal e AH moderada e grave), presença de AE nos EEGs de rotina e história médica de IPIs. Esses fatores são, desta forma, potenciais preditores de evolução clínica desfavorável. Na sua presença, deveríamos dar uma maior atenção a esses pacientes pela possibilidade de evolução para refratariedade. Este estudo também forneceu informações fundamentais para o melhor entendimento da fisiopatologia da ELTMF. Entendemos que, apesar de a nossa casuística não ser a ideal para definição de conceitos, os resultados obtidos sugerem que diferentes variáveis possam influenciar na gênese da ELTM e que talvez a fisiopatologia desta doença seja muito mais complexa do que inicialmente imaginado.

Conclusão

CONCLUSÃO

1. Pacientes com boa evolução clínica tendem a permanecer neste mesmo status.

2. Os pacientes refratários tendem a permanecer refratários, exceto quando submetidos à cirurgia.

3. A AH e a presença de atividade epileptiforme no EEG foram consideradas fatores preditivos de evolução desfavorável no seguimento clínico prospectivo.

4. A AH é provavelmente consequência de vários fatores etiológicos interagindo entre si, com graus variados de influência genética ou de fatores ambientais (IPIs).

5. AH parece ser a causa das crises, pelo menos na grande maioria dos pacientes.

6. Existe uma progressão da AH, que pelo menos em parte está associada às crises não controladas ao longo do tempo.

7. Os sinais de AH foram mais pronunciados nos pacientes refratários.

8. Entretanto, nem todos os indivíduos com sinais de AH na RM apresentavam crises refratárias, ou seja, grau de atrofia hipocampal, está associado à refratariedade, porém, por si só não explica a resposta ao tratamento. Outros fatores parecem estar envolvidos.

9. A atrofia de substância cinzenta detectada por MBV foi mais difusa em pacientes esporádicos que naqueles com história familiar de qualquer tipo de epilepsia.

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Apêndices

Apêndice 1

Anexo 1: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO, *Página 1 de 3*

Título do projeto: **Epilepsia de lobo temporal familial: Caracterização da evolução natural, progressão da atrofia hipocampal e resposta ao tratamento.**

Investigador principal: Dr. Fernando Cendes e Dra. Marcia E. Morita

OBJETIVO DA PESQUISA:

Eu _____ entendo que fui convidado (a) a participar em um projeto de pesquisa envolvendo pacientes com epilepsia. O objetivo geral do estudo é o de determinar a utilidade da Imagem e Espectroscopia por Ressonância Magnética nas epilepsias. A identificação e quantificação dessas anormalidades no cérebro, pode eventualmente melhorar o diagnóstico e levar a um melhor tratamento dessa doença. As informações médicas a meu respeito que forem obtidas para esse estudo, poderão ser compartilhadas com outros pesquisadores que trabalham com epilepsia. Podendo assim ser utilizadas eventualmente para outros fins de pesquisa sobre as epilepsias. O sigilo será mantido em todos os estudos colaborativos através da utilização de um número de código para a identificação dos indivíduos participantes.

A ressonância magnética é uma técnica capaz de produzir imagens de alta qualidade e resolução (nitidez) anatômica, assim como informações sobre a bioquímica dos tecidos. A ressonância magnética produz imagens em cortes que são parecidos com as imagens produzidas pela tomografia computadorizada, porém com maior resolução (nitidez) e sem a exposição aos raios X. Essas imagens também irão produzir informações bioquímicas que serão úteis para melhor definição do diagnóstico e tratamento. O objetivo principal desse estudo é determinar a importância dessas informações bioquímicas e estruturais.

PROCEDIMENTO:

Eu entendo que se concordar em participar desse estudo, os pesquisadores participantes farão perguntas a respeito dos meus antecedentes médicos e de minha família. Eu serei submetido a um exame físico neurológico para estabelecer meu estado clínico. Além disso, poderei ser submetido a um eletroencefalograma (EEG) além dos exames de ressonância magnética. Hospitalização não será necessária.

O procedimento de ressonância magnética é semelhante a uma tomografia. Eu fui informado que eu serei colocado em uma maca e serei movido lentamente para dentro do aparelho de ressonância magnética. Um alto falante dentro do campo magnético possibilita a minha constante comunicação com as pessoas responsáveis pelo exame. Durante todo o tempo o pessoal médico e paramédico pode me ver e ouvir, e eu posso ser removido(a) se for preciso; por exemplo, se durante o exame eu me sentir mal ou com claustrofobia. O procedimento pode durar entre 45 a 90 minutos. Durante a primeira parte do exame eu irei ouvir ruídos, tipo marteladas, por alguns minutos enquanto o aparelho faz as imagens do meu cérebro. O restante do exame será relativamente silencioso.

VANTAGENS:

Eu entendo que não obterei nenhuma vantagem direta com a minha participação nesse estudo e que o meu diagnóstico e o meu tratamento provavelmente não serão modificados. Contudo, os resultados desse estudo podem, a longo prazo, oferecer vantagens para os indivíduos com epilepsia, possibilitando um melhor diagnóstico e um tratamento mais adequado. Os resultados do meu exame de ressonância magnética ficarão a disposição dos médicos responsáveis pelo meu tratamento, e poderão ser úteis no futuro.

Título do projeto: **Epilepsia de lobo temporal familial: Caracterização da evolução natural, progressão da atrofia hipocampal e resposta ao tratamento.**

Investigador principal: Dr. Fernando Cendes e Dra. Marcia E. Morita

RISCO E DESCONFORTO:

O único desconforto relacionado a este exame é o ruído intermitente durante os primeiros 15 minutos. Depois disso o ruído será muito menor. O pessoal técnico providenciará tapa-ouvidos para me deixar mais confortável.

Uma das principais vantagens da ressonância magnética e que esta não utiliza raios X ou outro tipo de radiação ionizante, ao contrário de outros tipos de exame radiológicos. As imagens são obtidas graças a um campo magnético (imã), um transmissor e receptor de ondas de rádio e um computador que é utilizado para obter as informações bioquímicas e imagens da anatomia interna. Não existem efeitos nocivos associados com a ressonância magnética dentro das condições utilizadas atualmente.

REQUERIMENTOS

É **muito importante** informar aos médicos(as) e técnicos(as) caso eu tenha um **marca-passo cardíaco, um clipe de cirurgia para aneurisma cerebral ou qualquer outro objeto metálico em meu corpo,** que tenha sido implantado durante uma cirurgia ou alojado em meu corpo durante um acidente, pois estes podem parar de funcionar ou causar acidentes devido ao forte campo magnético que funciona como um imã muito forte. Eu também devo remover todos os objetos metálicos que estiverem comigo (relógio, canetas, brincos, colares, anéis, etc), pois estes também podem movimentar ou aquecer dentro do campo magnético.

SIGILO:

Eu entendo que todas as informações médicas decorrentes desse projeto de pesquisa farão parte do meu prontuário médico e serão submetidos aos regulamentos do HC- UNICAMP referentes ao sigilo da informação médica. Se os resultados ou informações fornecidas forem utilizados para fins de publicação científica, nenhum nome será utilizado.

FORNECIMENTO DE INFORMAÇÃO ADICIONAL:

Eu entendo que posso requisitar informações adicionais relativas ao estudo a qualquer momento. O Dr. Fernando Cendes, tel (019) 3521-8217 estará disponível para responder minhas questões e preocupações. Em caso de recurso, dúvidas ou reclamações contactar a secretaria da Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas-UNICAMP, tel. (019) 3521-7232.

RECUSA OU DESCONTINUAÇÃO DA PARTICIPAÇÃO:

Eu entendo que a minha participação é voluntária e que eu posso me recusar a participar ou retirar meu consentimento e interromper a minha participação no estudo a qualquer momento sem comprometer os cuidados médicos que recebo atualmente ou receberei no futuro no HC- UNICAMP.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO, *Página 3 de 3*

Título do projeto: **Epilepsia de lobo temporal familial: Caracterização da evolução natural, progressão da atrofia hipocampal e resposta ao tratamento.**

Investigador principal: Dr. Fernando Cendes e Dra. Marcia E. Morita

Eu confirmo que o(a) Dr(a)._____ me explicou o objetivo do estudo, os procedimentos aos quais serei submetido e os riscos, desconforto e possíveis vantagens advindas desse projeto de pesquisa. Eu li e compreendi esse formulário de consentimento e estou de pleno acordo em participar desse estudo.

_____
Nome do participante ou responsável

_____ _____
Assinatura do participante ou responsável data

_____
Nome da testemunha

_____ _____
Assinatura da testemunha data

RESPONSABILIDADE DO PESQUISADOR:

Eu expliquei a _____ o objetivo do estudo, os procedimentos requeridos e os possíveis riscos e vantagens que poderão advir do estudo, usando o melhor do meu conhecimento. Eu me comprometo a fornecer uma cópia desse formulário de consentimento ao participante ou responsável.

_____
Nome do pesquisador ou associado

_____ _____
Assinatura do pesquisador ou associado data

Faculdade de Ciências Médicas - Cidade Universitária "Zeferino Vaz" - Distrito de Barão Geraldo -
Campinas - SP - Brasil - CEP 13081-970 - C. P. 6111 - Tel: 55 (019)3521-7910 Fax (019) 3521-7483

Apêndice 2

Universidade Estadual de Campinas
Departamento de Neurologia

Nome		Data / /
Data de nascimento: / /	HC:	
peso	Altura	Sexo ( ) F ( ) M
Endereço		
Telefone		
Sd. Epiléptica:		
Inicio das crises (ano)		

Tipo de crises (descrição):

1. **aura:**
( ) epigastralgia ascendente ( ) não especifica – sintoma difícil de descrever
( ) medo/ansiedade outras auras emocionais ( ) ilusão de familiaridade deja vu
( ) ilusão de estranheza jamais vu ( ) gustatória ( ) olfativa ( ) sede
( ) autonômicos – dilatação de pupila, palpitação,arritmia ( )auditiva
( ) vertigem ( ) outros:
2. **alteração de consciência:**
( ) preservada ( ) alterada ( ) perda de consciência
3. **automatismos:**
( ) oromastigatórios ( ) manuais ( ) complexos
4. **ictal:**
( ) afasia ( ) anomia ( ) olhar fixo "arrest"
5. **sintomas motores:**
( ) movimentos clonicos braqui-faciais
( ) versão clonica da cabeça e olhos para ( )direita ( )esquerda
( ) postura distonica ( ) direita ( ) esquerda
( ) posição em 4 (cotovelo estendido e outro flexionado) – flexão ( ) direita ( ) esquerda
( ) generalização secundária
6. **pos-ictal:**
( ) alteração cognitiva ( )alt de memória ( )alteração de linguagem
( ) alteração de humor ( ) paralisia de Todd

Freq de crises ( ) CPS ( ) CPC ( ) CTCG	Data da última crise ( ) CPS : ( ) CPC : ( ) CTCG:

Doenças associadas

( ) crise febril, ( ) TCE , ( ) infecção de SNC, ( ) migrânea, ( ) hipoxia ( )depressão
outras:

Historia familiar de:
( )Crises (detalhar):

( ) Retardo mental:
( ) Outras doenças neurológicas:

Faculdade de Ciências Médicas - Cidade Universitária "Zeferino Vaz" - Distrito de Barão Geraldo -
Campinas - SP - Brasil - CEP 13081-970 - C. P. 6111 - Tel: 55 (019)3521-7910 Fax (019) 3521-7483

Heredograma detalhado com base em informações de :		
Uso de drogas anti epilépticas Atual: (Dose)		
Uso de drogas anti epilépticas Previas : (dose máxima tolerada e intolerância) ( ) carbamazepina ( ) fenobarbital ( ) acido valproico ( ) fenitoina ( ) clobazan ( ) trileptal ( ) lamotrigina ( ) topiramato ( ) outros:		
Efeitos adversos ( ) ganho de peso ( ) perda de peso ( ) hiperplasia gengival ( ) efeitos cosméticos ( ) rash cutâneo	( ) diplopia ( ) tontura/ ataxia ( )sonolência ( )náusea / vômito/ desconforto abdominal ( )tremor (sd parkinsoniana)	( ) dislipidemia ( ) polineuropatia ( ) hiponatremia ( ) aumento enz. hepáticas >3x ( ) leucopenia ( ) neutropenia
Obs ef colaterais:		
Outras medicações em uso:		
Historia de etilismo? ( ) sim ( )não		

Exame físico e neurológico ( ) normal ( ) alterado
Investigação: ( ) CT crânio. Data descrição:
Investigação: ( ) RNM : data descrição
Investigação: ( )EEG interictal ( ) OATD : Numero de EEGs: ( ) OATD Numero de EEGs: ( ) AOTBilat Numero de EEGs: ( )OLTD Numero de EEG:s ( ) OLTE Numero de EEGs: ( )OLTB Numero de EEGs: ( )outros: ictal (data / /)
Investigação: Spect: (data / /)) outros:
Avaliação neuropsicológica: data:
Coleta de sangue para DNA: ( )sim ( )não Data:
Classificação: (data) ( ) mesial ou ( ) lateral ( ) benigna, ( ) refrataria ou ( ) remissão ( ) refrataria pós-op outras obs>
Classificação prévia: 1ª avaliação (data) ( ) mesial ou ( ) lateral ( ) benigna, ( ) refrataria ou ( ) remissão ( ) refrataria pós-op

Exames de reavaliação: ( ) RNM : data
descrição

( )EEG interictal
( ) OATD : Numero de EEGs:
( ) OATD Numero de EEGs:
( ) AOTBilat Numero de EEGs:
( )OLTD Numero de EEG:s
( ) OLTE Numero de EEGs:
( )OLTB Numero de EEGs:
( )outros:

ictal (data / /)

Spect: (data / /)

outros:

Cirurgia S ( ) N ( )

Data / / local:
Anátomo patológico

Engel:
( ) classe I sem crises incapacitantes (Exceto as crises ocorridas nos pos op precoce 2 primeiras semanas)
A . completamente sem crises desde a cirurgia
B. apenas CPS não imcapacitantes desde a cirurgia
C. algumas crises incapacitantes após a cirurgia, porem sem crises incapacitantes por no mínimo 2 anos
D. crises generalizadas apenas durante a retirada de antiepilepticos
( ) classe II: raras crises incapacitantes quase sem crises
A. inicialmente sem crises incapacitantes porem agora tem raras crises
B. raras crises incapacitantes desde a cirurgia
C. algumas crises incapacitantes após a cirurgia porem com raras crises por no mínimo 2 anos
D. crises exclusivamente noturnas
( ) classe III melhora significativa
A. redução significativa das crises
B. intervalos sem crises prolongadas, maiores que metade do período de seguimento, porem menores que 2 anos.
( ) classe IV: sem melhora significativa
A. redução significativa das crises
B. sem alteração observável
C. piora das crises.
Medicação (redução)

Apêndice 3

Tabela - Anexo 1

Dados demográficos dos pacientes com ELTM familiar

ID	família	1a aval	2a aval	IPIs	idade RM1	idade RM2	T entre aval	início crises	CF	tipo crise	DAE	aura	EEG	atrofia hip	alt hipocampais	lado da atrofia	sexo	Engel
II3	f02	benigna	refratária	perinatal	28	37	109.44	3	sem	CPC; CPS; CTCG	sem	dejá vú	OL difusa	grave	sinal/forma/eixo	bil max D	M	
II2	f02	refratária	cirurgia	sem	34	44	109.92	7	sem	CPC; CPS; CTCG	FNT	visc/epig	AETD	grave	sinal/forma/eixo	direito	M	IIb
II1	f02	refratária	refratária	perinatal	37	47	109.93	3	sem	CPC; CPS; CTCG	CBZ, CLB	visc/epig	AETE	grave	sinal/forma/eixo	bil max E	F	
II5	f03	assint	assint	sem	34	42	99	NA	sem	NA	sem	assint	sem	leve	sinal	esquerdo	M	
II4	f03	assint	assint	TCE, perinatal	37	45	88.1	NA	sem	NA	sem	assint	sem	normal	forma/eixo	bilateral	M	
II2	f03	assint	benigna	sem	43	49	67.47	NA	sem	NA	sem	medo	sem	normal	forma/eixo	bilateral	M	
II1	f03	assint	benigna	sem	43	50	88.1	43	sem	NA	sem	medo; visc/epig	normal	leve	normal	esquerdo	F	
II6	f03	benigna	benigna	CF	29	37	96.13	14	CF	CPC; CPS; CTCG	FNT	dejá vú	AETE	leve	sinal	esquerdo	M	
II3	f03	refratária	cirurgia	CProlong	38	44	71.1	2	sem	CPC; CPS; CTCG	CBZ,FNT, CNZ	visc/epig	AETE	grave	sinal/forma/eixo	esquerdo	M	IIa
III3	f04	assint	assint	sem	14	20	68.47	NA	sem	NA	sem	assint	sem	leve	normal	esquerdo	M	
III2	f04	assint	assint	sem	17	23	68.47	NA	sem	NA	sem	assint	sem	leve	normal	esquerdo	M	
III1	f04	assint	assint	sem	18	24	68.47	NA	sem	NA	sem	assint	sem	normal	normal	normal	F	
III4	f04	benigna	remissão	perinatal, CF	8	17	114.53	3	CF	CPC; CPS; CTCG	sem	nausea, vômito	AETD	normal	normal	normal	M	
III5	f04	benigna	remissão	perinatal, CF	8	17	114.53	3	CF	CPS; CTCG	VPA	nausea, vômito	AETE	normal	normal	normal	M	
II1	f04	refratária	cirurgia	infec SNC	33	42	114.47	7	sem	CPC; CPS; CTCG	CBZ	visc/epig	AETE	grave	sinal/forma/eixo	esquerdo	F	IIb
II2	f04	remissão	remissão	perinatal	30	36	76.6	1	sem	CPC; CTCG	FNB	não sabe descrever	OLT bil	leve	forma/eixo	bilateral	F	
II8	f07	não classif	não classif	sem	32	41	108.27	7	sem	CPC; CTCG	sem	sem aura	sem	normal	forma/eixo	esquerdo	F	
II6	f07	refratária	refratária	perinatal	36	45	108.47	3	sem	CPC; CPS; CTCG	FNT	medo; jamais vú	AETbil	grave	sinal/forma/eixo	bil max D	F	
II3	f07	refratária	refratária	TCE	38	47	108.47	3	sem	CPC; CPS; CTCG	CBZ	dejá vú; visc/epig	AETD	grave	sinal/forma/eixo	direito	F	
II1	f07	remissão	remissão	TCE, CProlong	42	51	108	1	sem	CPC; CTCG	sem	sem aura	sem	mod	sinal/forma/eixo	bil max E	F	
II6	f08	assint	assint	sem	35	42	87.63	NA	sem	NA	sem	assint	sem	leve	forma/eixo	bilateral	F	
II1	f08	assint	benigna	sem	43	50	80.43	48	sem	NA	sem	panico/ ansied	AETE	normal	normal	normal	F	
III2	f08	não classif	não classif	CF	24	33	108.53	1	CF	CTCG	sem	sem aura	sem	normal	normal	normal	F	
II2	f08	não classif	não classif	sem	39	47	93.63	11	sem	CTCG	sem	sem aura	AETE	leve	sinal/forma/eixo	bilateral	F	
II4	f08	benigna	benigna	sem	36	44	87.63	15	sem	CPC; CPS	sem	visc/epig	sem	leve	forma/eixo	direito	F	
II3	f08	benigna	benigna	sem	36	45	107.4	13	sem	CPC; CTCG	FNT	não sabe descrever	OLTE	mod	forma/eixo	direito	F	
II5	f08	refratária	refratária	CProlong	33	41	95.23	4	sem	CPC; CPS; CTCG	FNT	visc/epig	AETbil	grave	sinal/forma/eixo	bil max D	F	
II3	f10	assint	assint	sem	48	56	104.52	35	sem	NA	sem	assint	sem	leve	normal	esquerdo	M	
III10	f10	assint	assint	sem	11	20	104.52	NA	sem	NA	sem	assint	sem	normal	normal	normal	M	
I1	f10	assint	assint	sem	73	82	108.72	NA	sem	NA	sem	assint	sem	grave	sinal/forma/eixo	bilateral	F	
III8	f10	não classif	não classif	sem	24	34	114.73	5	sem	CTCG	sem	sem aura	sem	leve	sinal/forma/eixo	bilateral	F	
II11	f10	não classif	não classif	sem	36	45	104.52	8	sem	CTCG	sem	sem aura	normal	normal	sinal/forma/eixo	bilateral	M	
III5	f10	não classif	não classif	sem	18	28	118.08	1	sem	CTCG	sem	sem aura	OLTD	normal	normal	normal	M	
II7	f10	não classif	não classif	sem	44	53	101.73	16	sem	CPC; CPS	DZP	visc/epig	sem	normal	normal	normal	F	
II5	f10	não classif	não classif	sem	47	56	114.7	12	sem	CTCG	sem	dejá vú	normal	normal	normal	normal	F	
III3	f10	benigna	remissão	sem	26	33	88.03	2	sem	CPC; CTCG	FNB	visc/epig	normal	leve	forma/eixo	bilateral	M	
III12	p10	benigna	benigna	sem	12	20	99	8	sem	CPC; CPS	CBZ	medo	sem	normal	normal	normal	F	
II14	f10	benigna	benigna	sem	32	40	87.83	6	sem	CPC; CPS; CTCG	FNB	olfatória; outra	sem	normal	normal	normal	F	
III4	f10	refratária	refratária	sem	24	32	93.77	14	sem	CPC; CPS; CTCG	CBZ	medo; olfatória	AETE	leve	normal	direito	F	
II10	f10	remissão	remissão	sem	38	45	87.83	18	sem	CPC; CPS	sem	sensação vivida	sem	leve	normal	direito	F	

Tabela - Anexo 1

Dados demográficos dos pacientes com ELTM familiar

ID	família	1a aval	2a aval	IPIs	idade RM1	idade RM2	T entre aval	início crises	CF	tipo crise	DAE	aura	EEG	atrofia hip	alt hipocampais	lado da atrofia	sexo	Engel
II1	f10	remissão	remissão	sem	50	57	88.03	9	sem	CPC; CPS; CTCG	sem	sensação vivida	sem	leve	normal	esquerdo	M	
III7	f10	remissão	remissão	CProlong	12	21	115.46	4	sem	CPC; CPS; CTCG	FNB	não sabe descrever	OLTD	leve	sinal/forma/eixo	esquerdo	M	
II4	f11	assint	assint	sem	9	16	81.93	NA	sem	NA	sem	assint	sem	leve	forma/eixo	esquerdo	F	
II3	f11	assint	assint	sem	12	19	81.94	NA	sem	NA	sem	assint	sem	normal	normal	normal	M	
II2	f11	não classif	não classif	CF	13	22	104.43	11m	CF	CPC; CTCG	sem	não sabe descrever	sem	normal	normal	normal	F	
II1	f11	refratária	refratária	sem	15	24	104.47	4	sem	CPC; CPS; CTCG	CBZ, FNB	visc/epig	AETE	grave	sinal/forma/eixo	esquerdo	F	
I1	f11	remissão	remissão	sem	34	42	96.8	2	sem	CPC; CPS; CTCG	FNB	visc/epig	normal	grave	sinal/forma/eixo	esquerdo	F	
II2	f12	assint	assint	sem	39	46	81.43	NA	sem	NA	sem	assint	sem	normal	forma/eixo	esquerdo	M	
II1	f12	refratária	cirurgia	sem	41	50	113.7	1	sem	CPC; CPS; CTCG	FNT	medo	AETE	grave	sinal/forma/eixo	bil max E	F	Ib
II4	f12	refratária	refratária	sem	31	35	48.14	8	sem	CPC; CPS; CTCG	CBZ, CLB	medo	AETbil	grave	sinal/forma/eixo	direito	F	
II2	f14	remissão	remissão	sem	47	55	100.7	12	sem	CPC; CPS; CTCG	sem	não sabe descrever	sem	normal	sinal/forma/eixo	esquerdo	M	
II4	f14	remissão	benigna	sem	39	47	100.7	18	sem	CPC; CPS; CTCG	FNT	dejá vú	OLTD	grave	sinal/forma/eixo	bil max E	M	
II3	f23	assint	assint	sem	35	43	94.73	NA	sem	NA	sem	assint	sem	leve	normal	bilateral	F	
II4	f23	assint	assint	sem	34	42	94.73	NA	sem	NA	sem	assint	sem	normal	forma/eixo	esquerdo	M	
II1	f23	benigna	remissão	sem	49	58	104.1	3	sem	CPC; CPS; CTCG	CLB	pânico/ ansied; visc/epig	AETD	leve	forma/eixo	bilateral	F	
I2	f23	benigna	benigna	sem	66	75	104.83	10	sem	CPC; CPS	sem	visc/epig	normal	mod	sinal/forma/eixo	bilateral	F	
II5	f23	refratária	cirurgia	sem	30	43	155.1	8	sem	CPC; CPS; CTCG	VPA, CBZ	dejá vú	AETE	grave	sinal/forma/eixo	direito	F	Ia
IV6	f26	assint	assint	sem	25	32	87.97	NA	sem	NA	sem	assint	sem	normal	normal	normal	M	
III1	f26	assint	assint	sem	48	53	67.43	NA	sem	NA	sem	assint	sem	normal	normal	normal	F	
IV8	f26	não classif	não classif	CF	20	29	104.4	infân	CF	CTCG	sem	sem aura	sem	normal	normal	normal	F	
V2	f26	não classif	não classif	CF e TCE	5	12	92.6	3	CF	CTCG	sem	sem aura	sem	normal	forma/eixo	esquerdo	M	
IV11	f26	não classif	não classif	sem	15	22	89.37	7	sem	CPC; CTCG	sem	sem aura	AETE	normal	normal	normal	M	
IV13	f26	não classif	não classif	sem	8	15	89.5	7	sem	CPC; CPS	sem	tontura; outra	sem	normal	normal	normal	M	
IV5	f26	benigna	benigna	sem	25	37	144.96	6	sem	CPC	CBZ	medo	sem	normal	normal	normal	F	
III18	f26	benigna	refratária	TCE	32	41	107.47	14	sem	CPC; CPS; CTCG	FNT	visc/epig	AETE	normal	normal	normal	F	
III11	f26	refratária	cirurgia	sem	27	36	112.23	2	sem	CPC; CPS; CTCG	CBZ	não sabe descrever	AETE (crise TE)	grave	sinal/forma/eixo	esquerdo	M	NA
III16	f26	remissão	remissão	sem	36	43	93.03	1	sem	CPC; CTCG	sem	sem aura	sem	leve	forma/eixo	esquerdo	M	
V1	f26	remissão	remissão	sem	8	16	94.67	8 m	sem	CPC; CTCG	sem	sem aura	normal	normal	normal	normal	M	
III20	f26	remissão	remissão	sem	29	39	120.63	18	sem	CPC; CPS	sem	tontura	normal	normal	normal	normal	M	
III13	f26	remissão	benigna	sem	42	50	105.37	5	sem	CPC; CPS; CTCG	sem	tontura	AETE	normal	normal	normal	F	
III14	f26	remissão	benigna	sem	41	50	115.5	3	sem	CPC	sem	tontura	sem	normal	normal	normal	M	
III4	f32	assint	assint	infec SNC	19	25	63.83	NA	sem	NA	sem	assint	OLTE	normal	normal	normal	F	
III2	f32	assint	benigna	perinatal	29	34	63.83	31	sem	NA	sem	panico/ ansied	AET bil	normal	normal	normal	F	
III1	f32	benigna	benigna	sem	27	36	107.37	17	sem	CPC; CPS; CTCG	CBZ	dejá vú; olfatória	AETE	normal	normal	normal	F	
III3	f32	benigna	benigna	sem	24	32	101.7	14	sem	CPC; CPS; CTCG	CBZ	olfatória	AETE	normal	forma/eixo	esquerdo	F	
II2	f45	assint	assint	sem	44	52	90.84	NA	sem	NA	sem	assint	sem	leve	forma/eixo	bil max E	M	
II8	f45	assint	assint	sem	33	40	92.33	NA	sem	NA	sem	assint	sem	leve	forma/eixo	esquerdo	F	
I1	f45	assint	assint	sem	65	73	89.73	NA	sem	NA	sem	assint	sem	normal	forma/eixo	esquerdo	F	
II9	f45	assint	assint	sem	33	38	69.07	NA	sem	NA	sem	assint	sem	normal	normal	normal	F	
II7	f45	assint	assint	TCE	34	41	90.97	NA	sem	NA	sem	assint	sem	normal	forma/eixo	bilateral	M	

Tabela - Anexo 1

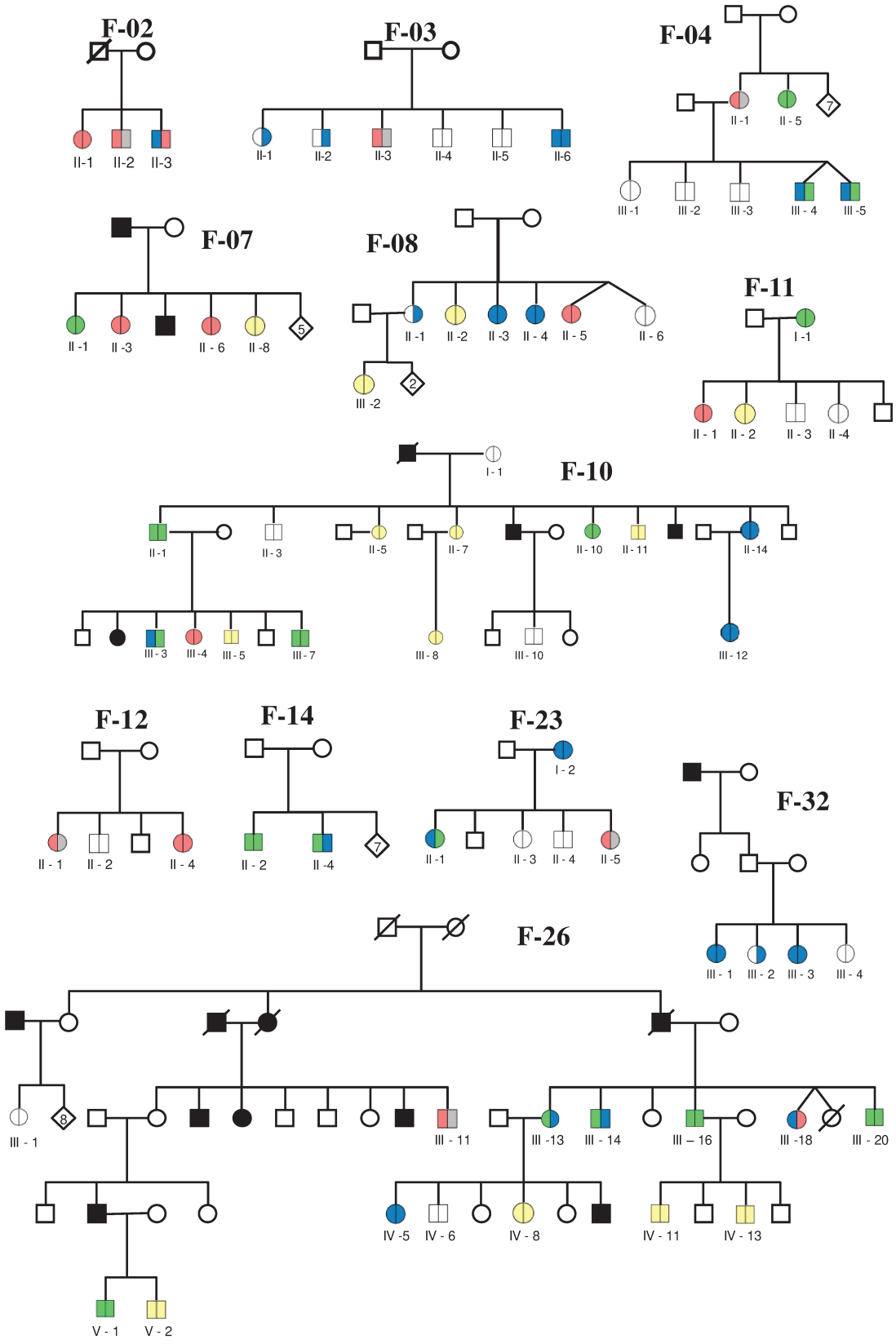
Dados demográficos dos pacientes com ELTM familiar

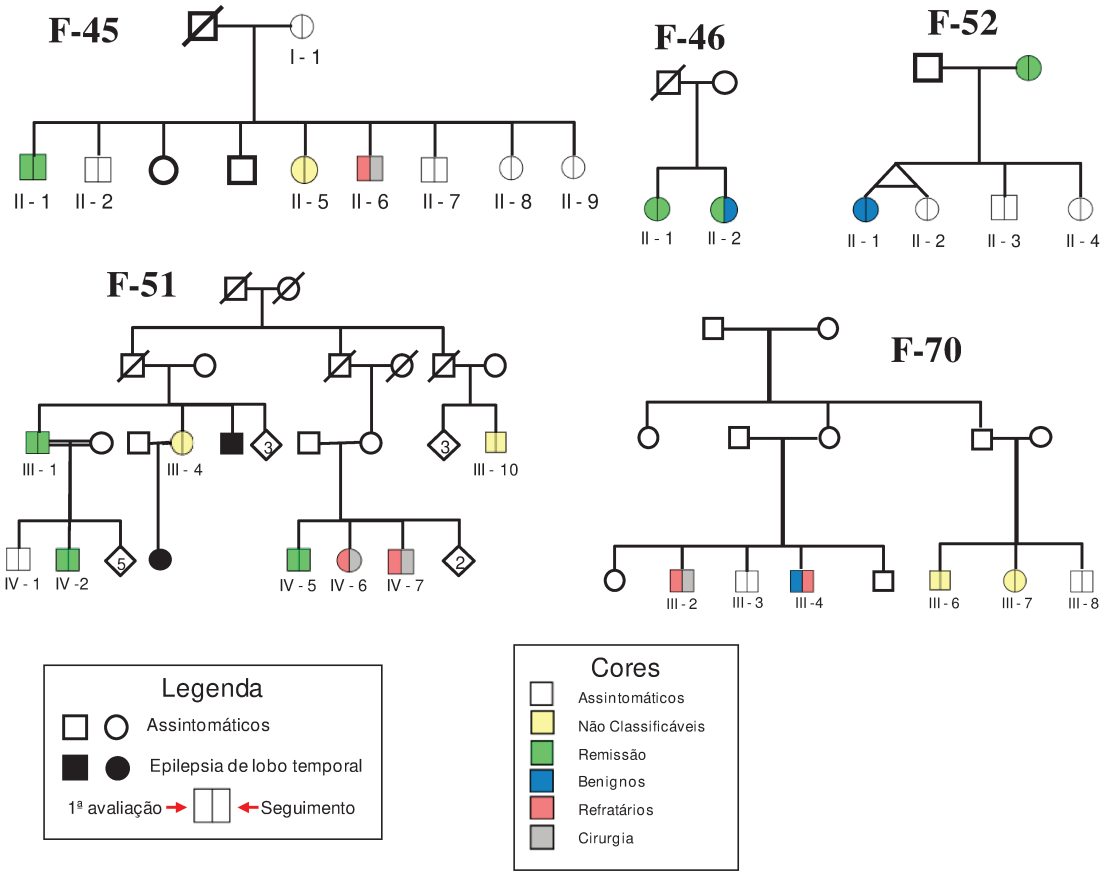
ID	família	1a aval	2a aval	IPIs	idade RM1	idade RM2	T entre aval	início crises	CF	tipo crise	DAE	aura	EEG	atrofia hip	alt hipocampais	lado da atrofia	sexo	Engel
II5	f45	não classif	não classif	sem	38	47	103.57	7	sem	CPS; CTCG	sem	visc/epig	OLTE	mod	sinal/forma/eixo	esquerdo	F	
II6	f45	refratária	cirurgia	sem	36	38	33.17	6	sem	CPC; CPS; CTCG	CBZ	medo; visc/epig	AET bil	grave	sinal/forma/eixo	esquerdo	M	IIa
II1	f45	remissão	remissão	sem	45	54	103.57	17	sem	CPC; CPS	sem	visc/epig	sem	normal	normal	normal	M	
II1	f46	remissão	remissão	sem	64	72	101.67	13	sem	CPC; CPS	CBZ	visc/epig	sem	leve	forma/eixo	esquerdo	F	
II2	f46	remissão	benigna	TCE	62	70	101.67	10	sem	CPC; CPS	CBZ	visc/epig	OLTE	normal	normal	normal	F	
IV1	f51	assint	assint	perinatal	41	47	66.53	NA	sem	NA	sem	assint	sem	normal	normal	normal	M	
III4	f51	não classif	não classif	perinatal, CF	58	64	65.5	30	sem	CTCG	FNB	sem aura	normal	grave	sinal/forma/eixo	esquerdo	F	
III10	f51	não classif	não classif	CF	57	62	69.17	infân	CF	CTCG	FNB, FNT	sem aura	sem	normal	forma/eixo	bilateral	M	
IV7	f51	refratária	cirurgia	sem	28	30	31.06	3	sem	CPC; CPS; CTCG	CBZ, FNB	visc/epig	AETE	grave	sinal/forma/eixo	bil max E	M	Ib
IV6	f51	refratária	cirurgia	sem	32	42	120	3	sem	CPC; CPS; CTCG	CBZ, CLB	arrepio	AETE	grave	sinal/forma/eixo	bil max E	F	Ia
IV2	f51	remissão	remissão	sem	19	25	69.13	4	sem	CPC; CPS; CTCG	sem	medo	sem	leve	sinal	direito	M	
IV5	f51	remissão	remissão	sem	37	43	82.77	2	sem	CPC; CPS; CTCG	sem	não sabe descrever	sem	mod	sinal/forma/eixo	bil max D	M	
III1	f51	remissão	remissão	sem	62	67	66.5	13	sem	CPC; CPS; CTCG	sem	tontura	sem	grave	forma/eixo	bilateral	M	
II3	f52	assint	assint	sem	35	40	68.47	NA	sem	NA	sem	assint	sem	leve	forma/eixo	bil max E	M	
II4	f52	assint	assint	sem	30	35	68.47	NA	sem	NA	sem	assint	sem	normal	normal	normal	F	
II2	f52	assint	assint	perinatal	36	42	68.47	NA	sem	NA	sem	assint	sem	normal	forma/eixo	direito	F	
II1	f52	benigna	benigna	perinatal	35	41	71.33	22	sem	CPC; CPS; CTCG	FNT, CLB	visc/epig	crise TD	mod	sinal/forma/eixo	direito	F	
III3	f70	assint	assint	sem	29	35	71.4	NA	sem	NA	sem	assint	sem	normal	normal	normal	M	
III8	f70	assint	assint	perinatal	18	24	70.13	NA	sem	NA	sem	assint	sem	normal	normal	normal	M	
III6	f70	não classif	não classif	CF	20	25	63.6	5	CF	CTCG	sem	não sabe descrever	OLTE	normal	normal	normal	M	
III7	f70	não classif	não classif	sem	24	28	50.8	11	sem	CTCG	sem	sem aura	AETE	normal	normal	normal	F	
III4	f70	benigna	refratária	sem	29	33	46.5	27	sem	CPC; CPS; CTCG	FNT	visc/epig	AET bil	normal	normal	normal	M	
III2	f70	refratária	cirurgia	sem	27	36	105.1	3	sem	CPC; CPS; CTCG	CBZ	medo	AETE	grave	sinal/forma/eixo	bil max E	M	IIb

Apêndice 3. Legenda: 1a aval, primeira avaliação; assint, assintomática; não classif, não classificáveis; 2a aval, segunda avaliação; perinatal, problema perinatal; TCE, traumatismo crânioencefálico; CF, crise febril; CProlong, crise prolongada; infec SNC, infecção do sistema nervoso central; T entre Aval, tempo entre avaliações; infân, infância; NA, não se aplica; CPC, crise parcial complexa; CPS, crise parcial simples; CTCG, crise tônico-clônica generalizada; DAE, droga antiepiléptica, FNT, fenitoína; CBZ, carbamazepina; CLB, clobazam; CNZ, clonazepam; VPA, ácido valpróico; FNB, fenobarbital; DZP, diazepam; visc, aura visceral; epig, aura epigástrica; ansied, ansiedade; EEG, eletroencefalograma; OL, onda lenta; AETD, atividade epileptiforme temporal direita; AETE, atividade epileptiforme temporal esquerda; AET bil, atividade epileptiforme temporal bilateral; OLT bil, onda lenta temporal bilateral; OLTE, onda lenta temporal esquerda; OLTD, onda lenta temporal direita; mod, moderada; bil, bilateral; Max, máxima.

Apêndice 4

Apêndice 4. Heredogramas




F-45
I - 1
II - 1
II - 2
II - 5
II - 6
II - 7
II - 8
II - 9
F-46
II - 1
II - 2
F-52
II - 1
II - 2
II - 3
II - 4
F-51
III - 1
III - 4
3
3
III - 10
IV - 1
IV -2
5
IV - 5
IV - 6
IV - 7
2
F-70
III - 2
III - 3
III -4
III - 6
III - 7
III - 8
Legenda
Assintomáticos
Epilepsia de lobo temporal
1ª avaliação
Seguimento
Cores
Assintomáticos
Não Classificáveis
Remissão
Benignos
Refratários
Cirurgia

Apêndice 5

frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE
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Longitudinal MRI volumetric evaluation in patients with familial mesial temporal lobe epilepsy

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Introduction: Studies have shown progressive cerebral damage in patients with refractory mesial temporal lobe epilepsy (MTLE). However, this has not been demonstrated in benign forms of MTLE such as familial mesial temporal lobe epilepsy (FMTLE). **Purpose:** To evaluate progression of hippocampal atrophy (HA) in patients with sporadic mesial temporal lobe epilepsy (SMTLE) and FMTLE by longitudinal Magnetic resonance images (MRIs) acquired with at least 7 months of interval. **Method:** We included 35 patients with FMTLE (25 classified as benign and 10 refractory) and 33 with SMTLE (4 benign and 29 refractory). All MRIs were analyzed by an investigator blind for clinical data. Hippocampal analyses were performed manually in coronal 3 mm thick T1 inversion recovery, using the software Scion Image®. Volumes were compared to those from a control group, and HA was determined for volumes below two standard deviations from the mean of controls. **Results:** The mean interval between the first (MRI1) and second MRI (MRI2) was 90 months for FMTLE and 45 months for SMTLE group. FMTLE group: volumetry demonstrated HA in 20 patients in MRI1 and in 23 patients in MRI2. There was significant progression of HA in FMTLE patients between MRIs in both benign and refractory FMTLE patients (benign FMTLE: right hippocampus, $p = 0.001$ and left hippocampus, $p < 0.001$; refractory FMTLE: right hippocampus, $p = 0.022$ and left hippocampus, $p < 0.010$). SMTLE group: volumetry demonstrated HA in 27 patients in MRI1 and in 29 patients in MRI2. In the group analysis, there was a significant reduction of the right ($p < 0.0001$) and left ($p < 0.0001$) hippocampal volumes during the follow-up period. Although the mean time between the MRIs in the FMTLE group was twice the time of the SMTLE group, the progression of volume loss was similar in both groups, indicating a slower progression in the FMTLE patients. Conclusion: FMTLE patients have progressive hippocampal volume reduction independently of seizure frequency although the progression of HA seems to be slower than in SMTLE.

Keywords: epilepsy, mesial temporal lobe epilepsy, magnetic resonance imaging, familial temporal lobe epilepsy, hippocampal sclerosis, seizures

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) is the most common type of partial epilepsy, and it is frequently associated with hippocampal sclerosis (HS; Gastaut et al., 1975; Bruton, 1988). Magnetic resonance images (MRI) signs of HS include hippocampal atrophy (HA), abnormal shape, loss of internal structure, and T2 hyperintense signal (Cascino et al., 1991; Cendes et al., 1993; Jackson et al., 1993).

The familial form of mesial temporal lobe epilepsy (FMTLE) was first described as a benign form of partial epilepsy (Berkovic et al., 1996; Kobayashi et al., 2001). Previous studies have demonstrated the presence of MRI signs of HS among patients with FMTLE and in some asymptomatic relatives (Kobayashi et al., 2001, 2002, 2003).

Clinical and experimental studies have tried to demonstrate the progression of hippocampal damage in patients with epilepsy and its association with refractory seizures with discrepant results (Kalviainen et al., 1998; Briellmann et al., 2002; Fuerst et al., 2003; Cendes, 2005; Cendes et al., 2005). However, there are no previous studies trying to demonstrate this association in patients with FMTLE.

The objective of this study was to investigate MRI volumetric abnormalities of hippocampus of patients with FMTLE and evaluate the possibility of progression of these abnormalities in patients with FMTLE and sporadic mesial temporal lobe epilepsy (SMTLE) in a longitudinal study with a prolonged follow-up.

MATERIALS AND METHODS

Patients from our epilepsy clinic with clinical and electroencephalographic diagnosis of MTLE and at least two MRIs obtained from October 1998 and January 2008 were followed prospectively and were included in this study.

All patients were interviewed in appointments every 3–6 months during the follow-up-period and seizure characteristics were constantly accessed. Patients were only included if they had seizures with typical mesial temporal lobe semiology and no atypical findings on the EEG.

According to clinical characteristics, patients were divided in two subgroups: (1) FMTLE (patients with at least two first or second degree relatives with MTLE as defined previously Kobayashi et al., 2001) and (2) SFMTLE (patients with no family recurrence).

Control group was composed of 14 health individuals, with no familial history of epilepsy and with two MRI performed with a minimum interval of 7 months.

Patients were also classified as benign or refractory based on the number of seizures presented on the year before the first MRI and in between the acquisition of both MRIs. Patients who had seizure remission, were seizure-free under AED or had sporadic seizures (three or less complex partial seizures per year) or had only simple partial seizures (typical MTLE auras) were considered as benign (for more detail, see Kobayashi et al., 2001).

Each patient had at least three routine EEG recordings with 30 min duration each, using the 10–20 electrode placement with additional temporal (T1, T2, and zygomatic electrodes) in an 18 or 32-channel digital EEG recording system, except for four patients with FMTLE who were under remission and refused to have follow-up EEGs. All patients with refractory seizures had abnormal EEG, showing epileptiform discharges over the anterior-mid temporal lobe region(s) coincident with the side of MRI showing signs of HS. In the FMTLE group, five patients who were under remission and one with rare seizures had normal routine EEGs (Kobayashi et al., 2001). The remaining FMTLE patients had abnormal EEG in one or both anterior-mid temporal lobe regions. All patients had typical history and semiology of mesial TLE (Cendes et al., 2005).

All patients signed an informed consent approved by the Ethic Committee of our institution before each MRI. Clinical data were collected prospectively. MRIs were performed in a 2T-scanner, with T1 and T2 acquisitions in three orthogonal planes. We used 3 mm T1-"inversion recovery" (T1-IR) coronal slices (flip angle = 200°; TR = 2800, TE = 14, inversion time = 840, matrix 130 × 256, FOV = 16 cm × 18 cm) for volumetric analysis.

Hippocampal volumes were determined manually (Watson et al., 1997) in the 3-mm T1-IR coronal images using Scion Image® software. The investigator who performed the volumetric and signal evaluation was blinded about patients' clinical data at the moment of MRI study. Hippocampal volumes were corrected by total intracranial volume for each patient to eliminate variation of the size of the brain (Watson et al., 1997). HA was determined for either total volumes or asymmetry index (smaller/larger ratio) below two standard deviations from the mean of the control group (Z-score < or = –2).

Statistical analysis was obtained with Systat 9® software. Chi-square test was used to determined differences of frequencies and paired t-test was used to compare the results between MRI1 and MRI2. The statistical significance was set to $p < 0.05$.

RESULTS

DEMOGRAPHIC ASPECTS

Familial mesial temporal lobe epilepsy

Thirty-five patients with FMTLE were included (9 men; mean age 41 years, minimum 17, and maximum 71). The mean interval between MRI1 and MRI2 was 90 months (ranging from 20 to 121 months). Twenty-five patients (71%) were classified as benign.

Sporadic mesial temporal lobe epilepsy

Thirty-three patients were included (14 men; mean age 36 years range from 21 to 70). The mean interval between MRI1 and MRI2 was 45 months (range from 7 to 85 months). Only four patients (12%) were classified as benign.

There was no difference of sex distribution or age between FMTLE and SMTLE individuals or between patients and controls.

VOLUMETRIC STUDY

Familial mesial temporal lobe epilepsy

Volumetric study demonstrated HA in 20 (57%) patients (6 right, 9 left, 5 bilateral) in MRI1 and in 23 (66%) patients (7 right, 11 left, 5 bilateral) in MRI2. Group analysis demonstrated a significant difference between the volumes of patients and controls for both the first and second MRI (t-test, MR1: right hippocampus, $p = 0.002$; left hippocampus, $p = 0.003$; AI, $p = 0.017$. MR2: right hippocampus, $p < 0.001$; left hippocampus, $p < 0.001$; AI, $p = 0.010$; **Figure 1**).

There was significant hippocampal volume reduction in the MRI2 when compared to MRI1 (paired t-test right hippocampus, $p < 0.001$; left hippocampus, $p < 0.001$; **Figure 2**).

When we divided the FMTLE patients in benign (25 (71%) individuals) and refractory (10 individuals), it was still possible to observe significant hippocampal volume reduction in the MRI2 when compared to MRI1 in both groups (paired t-test, benign FMTLE: right hippocampus, $p = 0.001$ and left hippocampus, $p < 0.001$; refractory FMTLE: right hippocampus, $p = 0.022$ and left hippocampus, $p < 0.010$). In the group of benign FMTLE, 14 patients (56%) had HA in MR1 and 16 (64%) in MRI2 and in the refractory group 6 (60%) had HA in MRI1 and 7 (70%; **Figure 3**).

Sporadic mesial temporal lobe epilepsy

Twenty-seven patients (82%) had HA in the MRI1. Two patients with normal first MRI presented HA at the second scan (29/33 patients, 88%). Group analysis demonstrated a significant difference between the volumes of patients and controls for both the first and second MRI (t-test MR1: right hippocampus, $p = 0.02$; left hippocampus, $p < 0.000$; AI, $p < 0.0001$. MR2: right hippocampus, $p = 0.004$; left hippocampus, $p < 0.001$; AI, $p < 0.001$; **Figure 1**).

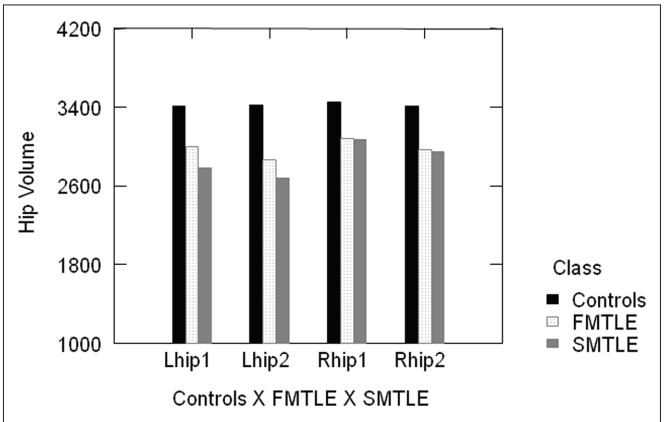

FIGURE 1 | Group analysis demonstrated significant difference of hippocampal volumes of controls and patients (FMTLE and SMTLE) for both the first and second MRI. Lhip1, left hippocampus in the first MRI; Lhip2, left hippocampus in the second MRI; Rhip1, right hippocampus in the first MRI; Rhip2, right hippocampus in the second MRI.

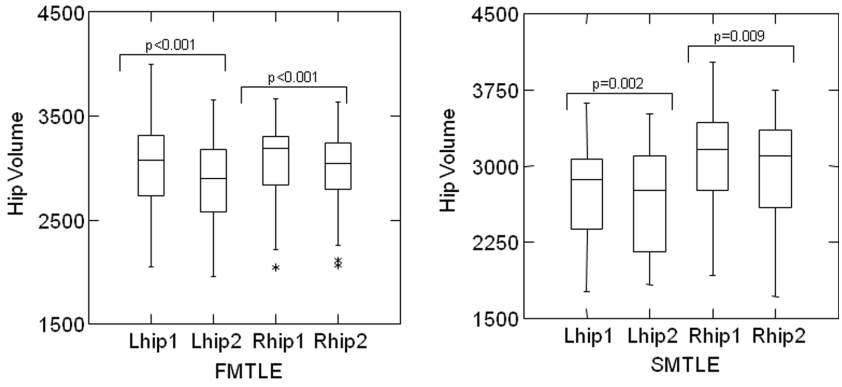

FIGURE 2 | Box and whisker plots: the bottom and top of the box represents the 25th and 75th percentile (the lower and upper quartiles, respectively), and the band near the middle of the box is the 50th percentile (the median). The "*" means outliers. Paired *t*-test comparing MRI1 and MRI2 showed a significant reduction of the right and left hippocampal volumes during the follow-up period in FMTLE and SMTLE groups. Lhip1, left hippocampus in the first MRI; Lhip2, left hippocampus in the second MRI; Rhip1, right hippocampus in the first MRI; Rhip2, right hippocampus in the second MRI.

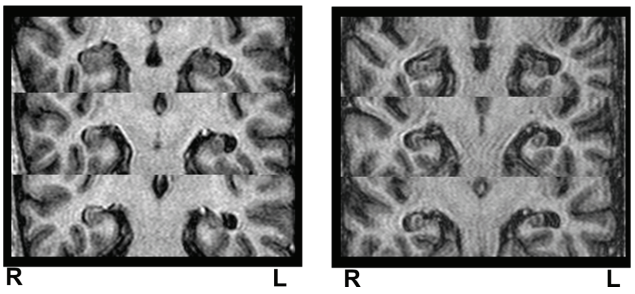

FIGURE 3 | Example of MRI acquired at time zero (MRI 1) and after 20 months (MRI 2), in a patient with FMTLE. Hippocampal volumetry demonstrated left hippocampal atrophy at MRI 1 (left *Z*-score = –2.33) and bilateral hippocampal atrophy at MRI 2 (left *Z*-score = –3.63 and right *Z*-score = –2.81), indicating progression of left hippocampal atrophy and the development of right hippocampal atrophy overtime. R, right side; L, left side.

Paired *t*-test comparing MRI1 and MRI2 showed a significant reduction of the right ($p = 0.009$) and left ($p = 0.0025$) hippocampal volumes during the follow-up period (**Figure 2**).

We also subdivided the SMTLE patients in benign [4 (12%) individuals; 2 (50%) with HA in MR1 and 3 (75%) with HA in MRI2] and refractory [29 individuals; 25 (86%) with HA in MR1 and 26 (90%) with HA in MRI2]. However, the number of patients in the benign group was too small for statistical analysis.

Although the mean time between the MRIs in the FMTLE group was twice the time of the SMTLE group, there was no difference of degree of volume reduction in MRI2 among the two groups (FMTLE or SMTLE; *t*-test, right hippocampus: $p = 0.886$, and left hippocampus: $p = 0.598$).

Control group

Paired *t*-test comparing MRI1 and MRI2 failed to demonstrate a significant reduction of the right ($p = 0.259$) or left ($p = 0.888$) hippocampal volumes during the follow-up period in the control group (**Figure 1**).

DISCUSSION

As demonstrated by previous studies, we observed that FMTLE patients commonly have HA detected by post-processing MRI techniques (57–66%; Kobayashi et al., 2001, 2003), although this is less frequent than observed in SMTLE (82–88%; Watson et al., 1997; Fuerst et al., 2003; Cendes et al., 2005). What we were able to demonstrate for the first time is that, like in SMTLE (Watson et al., 1997; Pitkänen et al., 2002; Cendes, 2005; Bonilha et al., 2006; Bernhardt et al., 2009; Coan et al., 2009), FMTLE patients have hippocampal volume reduction over time, independently of seizure frequency.

Familial mesial temporal lobe epilepsy is considered a benign form of epilepsy, although some patients present with medically refractory seizures and require surgical treatment (Berkovic et al., 1996; Kobayashi et al., 2001, 2002, 2003). In the present study the majority of patients had a benign form of FMTLE (71%) as expected, while the majority of SMTLE individuals were refractory (88%). Previous clinical (Cendes, 2005; Bonilha et al., 2006; Coan et al., 2009) and experimental (Bonilha et al., 2006) studies of refractory MTLE have shown progressive atrophy of mesial temporal lobe structures and also of neocortical structures (Bonilha et al., 2006; Bernhardt et al., 2009; Coan et al., 2009) over time and some also correlated the seizure frequency with the progression of damage (Kalviainen et al., 1998; Briellmann et al., 2002; Fuerst et al., 2003; Cendes, 2005; Cendes et al., 2005). However, there are no studies showing unequivocal evidence of progressive damage in patients with benign forms of epilepsy, such as FMTLE.

We made an option, in this study, to consider as benign those patients with up to three complex partial seizures per year or only simple partial seizures, although this definition is subjective (Kobayashi et al., 2001). However, for better understanding of MTLE some classification must be used to try to clarify these gaps (Labate et al., 2011). We hypothesized that seizure frequency has influence on the evolution of the disease, as demonstrated by previous clinical, experimental, neuroimaging, and neuropsychological studies (Kalviainen et al., 1998; Pitkänen et al., 2002; Fuerst et al., 2003; Cendes, 2005; Bonilha et al., 2006; Bernhardt et al., 2009; Coan et al., 2009). Although our classification is arbitrary,

it allowed the separation of two extremes of seizure control and to evaluate their neuroimaging evolution. We may also add the fact that those patients who presented only simple partial seizures during the follow-up and were classified here as benign, had typical psychic or autonomic auras of MTLE which were not disabling.

Although FMTLE is described as a benign condition, in our group a significant number of patients had frequent seizures. With this classification (benign X refractory) our main purpose was to clarify if refractory FMTLE had the same evolution as refractory SMTLE. Indeed, when we analyzed the progression of HA over time in the two groups (benign FMTLE and refractory FMTLE) both had equivalent hippocampal volume reduction. Unfortunately, we were not able to determine if the benign SMTLE patients had significant progression of HA, once the number of individuals in this group was too small.

It would be important to analyze these individuals in smaller groups concerning, for instance, sex, age of epilepsy onset or duration of epilepsy, history, and type of initial precipitating injury. However, the number of patients in these subgroups would be too small for the statistical analysis. We strongly believe that further studies, with a larger number of patients and more detailed MRI evaluation, as the measure of other mesial temporal structures would be interesting.

The fact that not only the FMTLE patients had a significant loss of hippocampal volume along the time, but also when we subdivided this group, the benign FMTLE individuals also had significant progression of HA is an important finding. We may speculate that the hippocampal volume reduction over time is not clinically significant to seizure control in FMTLE patients, since the group of benign individuals continued to be well controlled (most of them were seizure-free with or without medication) during this period.

Our results also demonstrated that although the mean time between the MRIs in the FMTLE group was twice the time of the SMTLE group, the degree of volume reduction was not different between the two groups. If the progression of HA was similar in both groups, we would expect to find more pronounced volume reduction in FMTLE. We may hypothesize that this slower hippocampal reduction in FMTLE happened because of the difference of refractory patients in both groups (88% of SMTLE vs 29% of FMTLE), although the benign FMTLE also had significant volume reduction. Most probably the mechanisms related to the progression of damage in these two groups, SMTLE and FMTLE, are diverse with an important contribution of the genetic characteristics in FMTLE. This is corroborated by a recent paper from our group emphasizing the stronger environmental influence in patients with MTLE without a family history that could influence the more widespread brain structural abnormalities and worse IQ performance found in SMTLE patients (Yasuda et al., 2010).

We acknowledge that the significant difference in the interval of the MRIs between FMTLE and SMTLE is a possible limitation of our study; however, it propitiated an interesting result. The difference in the interval of MRIs can be explained mainly because the patients with refractory seizures were on the waiting list for surgical treatment and it was not ethical to wait too long to do a second MRI before surgery. On the other hand, as the majority of FMTLE individuals were benign, they could have a second MRI after a longer interval. Additionally, we had the prior hypothesis that the FMTLE patients would have no or very mild progression, since most of them had a "benign" clinical course (remission, seizure control, or rare seizures). If they had two MRIs with a short interval and we did not find a significant hippocampal volume difference we would be left with the question that it could have been due to the short interval or low seizure frequency in this group.

The fact that seizures are responsible for additional damage in patients with epilepsy is controversial (Cendes, 2005). While some neuroimaging studies describe a significant relation of seizure frequency and cerebral volume reduction of patients with refractory epilepsy (Bonilha et al., 2006; Bernhardt et al., 2009; Coan et al., 2009), other studies did not agree, including a post-mortem study that did not find a relationship between seizure frequency and hippocampal neuronal loss (Thom et al., 2005). In contrast, a recent study demonstrated that MTLE patients with refractory seizures had more significant and diffuse gray matter damage than those that were seizure-free or had remitting–relapsing evolution (Bilevicius et al., 2010). This difference maybe predominantly related to the heterogeneity of patients included in each study and the different techniques used to address the progression of atrophy.

Actually, it is important to address that MTLE is not a single disease (Cendes et al., 2005; Berg, 2008) but a clinical and electroencephalographic syndrome. The diverse prognostic and evolution seen on different MTLE patients may be related to different etiological factors or diverse initial precipitating injuries. Studies with a larger number and more homogeneous individuals are necessary to clarify these questions.

It is most likely that seizure frequency causes further hippocampal damage and consequently volume reduction in only some types of epilepsies or epileptic patients. In addition, seizure types and duration of habitual seizures may influence neuronal damage differently according to the basic etiological mechanism implicit on each different individual. When we focus on MTLE we are surely evaluating epilepsies with diverse etiologies and the causes of neuronal damage will certainly be different, and may not necessarily be directly related to the seizures *per se*, but to the underlying mechanisms of seizure generation. Therefore, this could explain the fact that a phenomenologically similar seizure type (with similar frequency) in two different patients may cause more damage in one than in the other.

In this specific study, we did not aim to analyze other MRI features of HS, such as T2 hyperintense signal, loss of internal architecture, or abnormal hippocampal axis. This more subtle abnormalities would require a bigger number of patients to show significant results. Indeed, the most reliable MRI finding of HS is the presence of HA combined with hyperintense T2 signal. If we analyze any of the MRI findings isolated, HA is the most reliable MRI feature of HS. Hyperintense T2 signal can be present in some patients without atrophy, but in a very small proportion of patients. In addition, when we take any of these two findings isolated, there is a higher chance of false positives for hyperintense T2 signal than for atrophy (Cendes and Cascino, 2010; Labate et al., 2010).

In summary, FMTLE patients have hippocampal volume reduction over time independently of seizure frequency although this progression of damage seems to be slower than what occurs in SMTLE.

Up to now, there is important evidence on literature that epilepsy is a progressive disorder with variable severity. It is important to define in which particular group of patients it happens and what the specific causes of this progression are.

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Apêndice 6

Relationship between environmental factors and gray matter atrophy in refractory MTLE

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ABSTRACT

Objective: To investigate clinical, neuropsychological, and MRI abnormalities (gray matter atrophy [GMA] and white matter atrophy [WMA]) in surgical mesial temporal lobe epilepsy (MTLE) patients with and without familial antecedent for epilepsy.

Methods: A cohort study including 69 operated patients with unilateral MTLE, divided into a group of 29 patients (mean age 35.8 ± 10.4 years) with a negative family history (FH) of epilepsy and a group of 40 patients (32.8 ± 10 years) with a positive FH. We performed voxel-based morphometry (VBM) on preoperative MRIs and investigated possible clinical and neuropsychological differences between the 2 groups. We also performed VBM and *t* tests to compare the patients' groups with normal controls.

Results: The negative-FH group had lower IQ scores ($p = 0.004$), performed poorer on the Boston Naming Test ($p = 0.02$) and on delayed recall ($p = 0.03$), and presented a more prominent asymmetry index of hippocampal volume ($p = 0.04$) and more frequent initial precipitating injuries ($p = 0.023$). VBM showed a more restricted pattern of GMA in the positive-FH group and a more bilateral and widespread pattern of GMA in the negative-FH group, involving thalami, temporal, frontal, parietal, and occipital lobes. WMA was widespread and bilateral in both groups.

Conclusions: The more widespread structural voxel-based morphometry abnormalities and worse IQ performance identified in the negative–family history (FH) group may result from a stronger environmental influence, including initial precipitating injuries. This is further support for the hypothesis that hippocampal sclerosis in mesial temporal lobe epilepsy with positive FH is determined by a stronger genetic predisposition with less influence of environmental factors compared with patients in the negative-FH group. ***Neurology*® 2010;74:1062–1068**

GLOSSARY

AED = antiepileptic drug; **AI** = asymmetry index; **BNT** = Boston Naming Test; **FH** = family history; **FMTLE** = familial mesial temporal epilepsy; **GM** = gray matter; **GMA** = gray matter atrophy; **HA** = hippocampal atrophy; **IPI** = initial precipitating injury; **MNI** = Montreal Neurological Institute; **MTLE** = mesial temporal lobe epilepsy; **SPM** = statistical parametric map; **VBM** = voxel-based morphometry; **WM** = white matter; **WAIS-R** = Wechsler Adult Intelligence Scale–Revised; **WMA** = white matter atrophy; **WMS-R** = Wechsler Memory Scale–Revised.

Mesial temporal lobe epilepsy (MTLE) is one of the most common forms of refractory epilepsy referred to surgical treatment. Some of these patients do not present family history (FH) of epilepsy up to 3 generations (also referred to as sporadic MTLE), whereas others present a positive FH of seizures that may vary from a well-characterized pattern of familial recurrence of MTLE (defined as familial mesial temporal epilepsy [FMTLE])[1] to the occurrence of other types of epilepsy in 1 or a few relatives, which is not sufficient to characterize a specific genetic syndrome. The development of hippocampal sclerosis in patients with FMTLE does not seem to be only the result of recurrent seizures but is determined by a strong genetic predisposition.[1] Some of these patients develop refractory seizures, and surgical treatment offers a good outcome when unilateral or clearly asymmetric hippocampal atrophy (HA) can be identified on

Supplemental data at www.neurology.org

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MRI.[2,3] Patients with familial or sporadic MTLE present similar clinical features, and the presurgical investigation can be performed without distinction between the groups.[2]

In refractory MTLE, areas with gray matter atrophy (GMA) and white matter atrophy (WMA) have been identified in temporal and extratemporal regions[4] and may be related to the cognitive impairment present in most of these patients.[5] Surgical treatment offers the chance of functional recovery in addition to seizure control[6] as well as postoperative metabolic recovery.[7,8]

In this study, we aimed to investigate differences in extratemporal GMA and WMA between groups of MTLE patients with and without an FH of epilepsy, as well differences in the IQ performance and the presence of initial precipitating injuries (IPIs).

METHODS

Patients. We included 69 normal controls (39 women; mean age ± SD, 34.3 ± 11.1 years) and 69 consecutive patients with MTLE (42 women; mean age ± SD, 34.1 ± 10.2 years) who underwent surgical treatment at our institution. Patients underwent a comprehensive preoperative investigation that confirmed clinical and EEG features of unilateral MTLE and MRI evidence of hippocampal sclerosis.[9,10] We included only patients with unilateral HA, with or without hyperintense T2 signal and loss of internal structure, detected by visual analyses on routine MRI with thin coronal cuts and confirmed by hippocampal volumetry according to an anatomic protocol,[11] absence of contralateral mesial temporal atrophy or signal changes, and absence of any other suspected MRI abnormalities, therefore excluding MTLE patients with dual pathology, normal MRI, and bilateral HA. Clinically, they presented features of typical MTLE,[10] including clear-cut interictal EEG epileptiform discharges in the anterior-infero-mesial temporal region; simple partial or complex partial seizures or both, with typical mesial temporal lobe origin such as rising epigastric sensations, psychic phenomena, complex partial seizures with staring, oroalimentary automatisms, dystonic posturing of 1 hand and postictal confusion, and no suggestion of extratemporal epilepsy syndrome. We confirmed failure of seizure control with at least 2 antiepileptic drug (AED) regimens and a seizure frequency of at least 1 seizure per month over the year before surgery. We considered as possible IPIs the following events: febrile seizures, evidence of birth trauma, head trauma with unconsciousness, meningitis, meningoencephalitis, and other remote infections, including neurocysticercosis.

Our routine outpatient presurgical investigation included MRI (full protocol described below), EEG, and neuropsychological and psychological assessments. We also performed video-EEG and ictal SPECT for patients with unclear origin of ictal discharges. We excluded 23 patients with significant artifacts on either preoperative scan; therefore, the patients studied here do not represent our surgical series of MTLE.

One investigator with expertise in MRI and epilepsy (F.C.) performed the diagnosis of unilateral HA and other signs of hippocampal sclerosis by visual analyses, which were confirmed after surgery in all patients with sufficient tissue available for pathology, according to typical histologic findings: gliosis and neuronal loss in dentate gyrus, CA1 and CA3, with relative sparing of CA2.[12] Sixteen patients had anterior temporal lobe resection with amygdalohippocampectomy, and 53 had selective transsylvian amygdalohippocampectomy.

Standard protocol approvals. This study was approved by the ethics committee of our institution, and all patients gave us a written informed consent for this study.

Clinical classification. Patients were separated into a group of 29 patients with a negative FH of epilepsy (11 men, aged 35.8 ± 10.4 years) and a group of 40 patients with a positive FH (16 men, aged 32.8 ± 10 years).

We used a structured questionnaire for all patients to investigate the occurrence of epilepsy in their families.[1] In the positive-FH group, we confirmed the FMTLE syndrome for 9 patients, whereas for the remaining 31 patients, we were unable to confirm MTLE in the affected relatives, because they lived too far away from our center to be evaluated. Therefore, it is possible that some of the affected family members of these patients had different phenotypes.[13] A positive FH was defined here when there was at least 1 other individual (first- or second-degree relative) with epilepsy in the family of the operated patient, and a negative FH was considered if the operated patient was the only individual presenting seizures in the 3 most recent generations of the whole family.

Neuropsychological evaluation. The neuropsychological preoperative investigation included the Wechsler Adult Intelligence Scale–Revised (WAIS-R) to estimate IQ, the Boston Naming Test (BNT), the Wechsler Memory Scale–Revised (WMS-R), the Logical Memory and Verbal Paired Associates and Figural Memory, Visual Reproduction, and Visual Paired Associates. We did not use the same MRI control group for neuropsychological data. All tests were adapted for our population.[5]

Images. ***Acquisition.*** The MRIs were acquired in a 2-T scanner (Elscint Prestige) using the following parameters: 1) sagittal T1 spin echo; 2) coronal images: a) T2-weighted and proton density fast spin echo and b) T1-weighted inversion recovery; 3) axial images: a) T1-weighted gradient echo and b) fluid-attenuated inversion recovery; and 4) T1-weighted 3-dimensional gradient echo with 1-mm isotropic voxels[14] (details in appendix e-1 on the Neurology® Web site at www.neurology.org).

We used the same 3-dimensional protocol for patients and for healthy controls.

MRI volumetric analysis. We performed manual volumetry of the hippocampi[11] in all patients and controls using DISPLAY (David McDonald, www.bic.mni.mcgill.ca/software) and obtained the asymmetry index (AI) for each subject (defined as the ratio of the smaller by the larger hippocampus). Volumes or AIs that were 2 SDs below the mean values of controls were considered as evidence of HA. Both hippocampal volumes and AIs were transformed into *z* scores (standardized scores defined by the number of SDs away from the mean of control group) to facilitate presentation of the data.

Preprocessing for voxel-based morphometry. We used MRIcro software (www.mricro.com) to convert the original DICOM format to ANALYZE format,[15] mark the anterior commissure (for the normalization process), and flip the brains with right HA to left to simultaneously study right and left hippocampal atrophies, avoiding left-to-right cancellations.

Voxel-based morphometry. To perform the optimized version of voxel-based morphometry (VBM),[16] we used the SPM2 software (www.fil.ion.ucl.ac.uk) on MATLAB7.0 (The Math-

Works, Inc., Natick, MA). The standard VBM uses the following sequence of processes: normalization, segmentation, and smoothing of images. The optimized VBM included a "modulation" step after segmentation, which corrects volume changes that occur during nonlinear spatial normalization. This optimization of VBM is used when gray matter (GM)/white matter (WM) volume is more important than GM/WM concentration, and it may reveal more subtle abnormalities in GM volume than with the standard version of VBM.

Statistical analysis. We used SYSTAT12 (Systat Software Inc., Chicago, IL) to analyze clinical variables from groups of patients and controls, applying the *t* test with the Bonferroni correction to compare continuous data and Fisher exact test for categorical variables.

The statistical analyses of VBM were performed with SPM2 software, including the *t* test to compare groups of patients with the control group and regression analysis to study the relation between GM and IQ scores. We used the *t* test to assess areas of specific GM and WM reduction, based on the probability of a voxel being GM or WM. This analysis included proportional threshold masking and implicit masking.

A regression analysis was performed between the total volume of GM and WM using individual IQ score as the regressor. To control for multiple comparisons, we applied family-wise error correction with a p threshold of 0.05.[17] To focus the analyses on where the effects were most intense, we applied an extent threshold to look for clusters with at least 50 contiguous voxels.

The output for each comparison was a statistical parametric map (SPM) of the *t* statistic (SPM *t*), which was transformed to a normal distribution map (SPM *z*). The statistical significance threshold for the resulting SPM *t* was set at $p < 0.05$ (FDR corrected).

The Montreal Neurological Institute (MNI) coordinates resulting from the SPM outputs were confirmed visually and then transformed into anatomical names using the routines MNI Space Utility and Talairach Space Utility on SPM2 (for the algorithms, see http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html).[18]

We used the built-in SPM2 routine display_slices (http://imaging.mrc-cbu.cam.ac.uk/imaging/DisplaySlices) to show the statistical maps from the SPM overlaid on coronal images of an SPM2 smoothed T1 MRI template[19] with the corresponding *T* value bar for each map (simultaneous GM and WM results).

Table 1 Clinical data from groups with positive and negative family history of epilepsy[a]

	Positive FH	Negative FH	*p* Value
No. of women	24 (60)	18 (62)	1
Left side	19 (48)	16 (55)	0.63
Age at seizure onset, y	5.4 ± 5	5.7 ± 4.2	0.78
Education, y	8.3 ± 4.24	6 ± 4.1	0.03
Seizure frequency/mo	10 ± 9	10 ± 8	0.7
z Scores of asymmetry index	−5.8 ± 3.6	−7.5 ± 2.6	0.04
Duration of epilepsy, y	27.6 ± 10.8	30.2 ± 10.9	0.33
AED polytherapy	35 (87.5)	27 (93)	0.39
IPI	10 (25)	15 (51)	0.023
Age at surgery, y	32.8 ± 10.1	35.8 ± 10.4	0.23
Surgical outcome			0.23
Engel IA[b]	21 (53)	15 (52)	
Engel IB–II[b]	12 (30)	12 (41)	
Engel III–IV[b]	7 (17)	2 (7)	
Follow-up, mo	57.7 ± 32.1	66.4 ± 29.3	0.25

Abbreviations: AED = antiepileptic drug; FH = family history; IPI = initial precipitating injury.
[a]Values are mean ± SD or n (%).
[b]χ^2 test; no differences between groups.

RESULTS No differences were observed between groups of controls and patients with regard to gender ($p = 0.73$) or age ($p = 0.92$).

The patient groups presented similar preoperative clinical characteristics, although the negative-FH group had a lower educational level ($p = 0.03$), more accentuated hippocampal AI ($p = 0.04$), and a higher incidence of IPI ($p = 0.023$) (table 1).

In neuropsychological tests, the negative-FH group performed less well on the WAIS-R test ($p = 0.004$), BNT ($p = 0.02$), and WMS-R delayed recall ($p = 0.03$) (table 2).

Gray matter atrophy. Based on the comparison with controls, the positive-FH group showed areas with GMA in the ipsilateral occipital, parietal, insula, thalamus, and temporal lobe (encompassing the hippocampus, amygdala, parahippocampal and superior temporal gyri) and in the contralateral frontal lobe (figure e-1A and table e-1). The GMA in the negative-FH group, on the contrary, showed a bilateral and widespread pattern, encompassing the entire ipsilateral temporal lobe, as well as areas in the thalami, cerebellum, occipital, parietal, and frontal lobes. In the contralateral hemisphere, GMA was identified in the frontal, temporal, and parietal lobes (figure e-1B and table e-2).

The *t* test between groups confirmed more widespread GMA in the negative-FH group, mainly in the contralateral hemisphere, involving both temporal and extratemporal regions (figure; table e-3).

White matter atrophy. The pattern of WMA was bilateral and widespread in both groups, but less pronounced in the positive-FH group (figure e-1A and table e-4) than in the negative-FH group (figure e-1B and table e-5) when each group was compared with the controls. However, the *t* test on SPM did not show differences in WMA between the positive-FH and negative-FH groups.

Correlation between IQ score and gray matter. There were no significant correlations between the IQ score and amount of GM in each voxel for either group.

DISCUSSION In agreement with previous studies,[13] patients presented early onset of seizures (approximately 5 years),[2,20] a long duration of epilepsy (approximately 30 years),[2] and a high frequency of seizures,[21] and most of them were under AED poly-

Table 2 Results from neuropsychological evaluation (*z* scores, except on Wechsler Adult Intelligence Scale)[a]

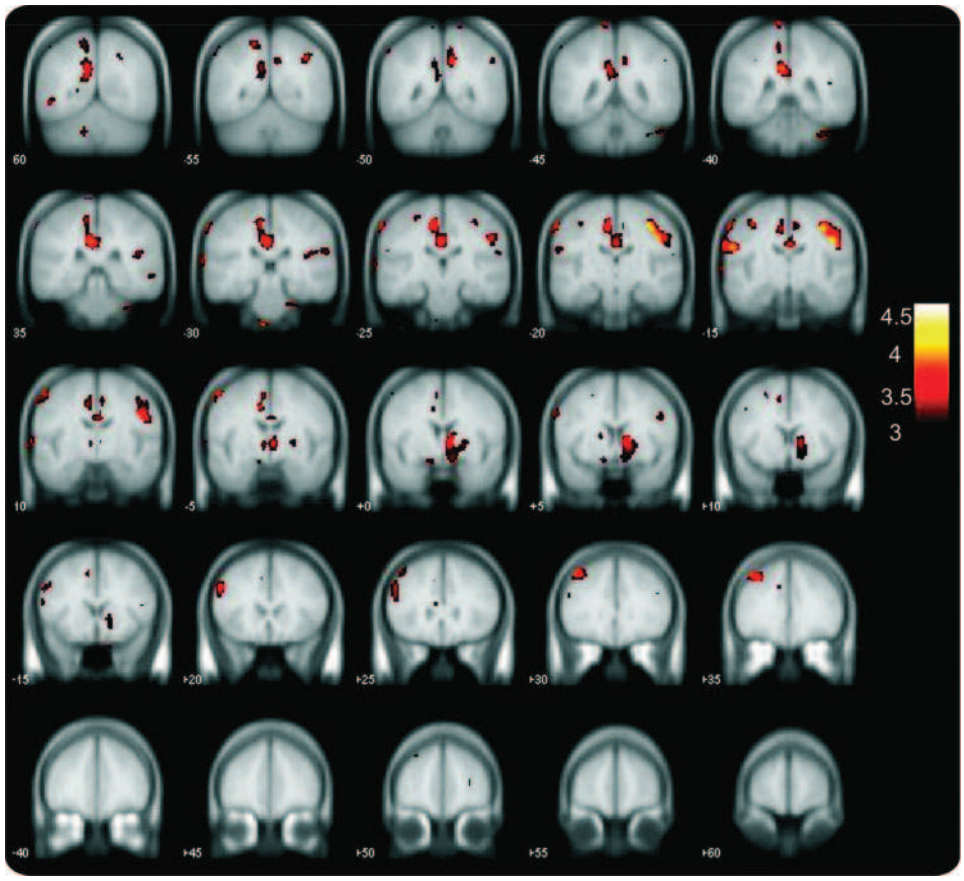
	Positive FH	Negative FH	*p* Value
WAIS-R IQ	92.85 ± 8.69	86.15 ± 9.33	0.004
BNT	−1.93 ± 2.78	−3.95 ± 4.03	0.02
WMS-R general memory	−0.32 ± 1.25	−0.8 ± 1.14	0.13
WMS-R verbal memory	−0.26 ± 1.3	−0.54 ± 1.12	0.35
WMS-R visual memory	−0.36 ± 0.97	−0.82 ± 1.06	0.08
WMS-R delayed recall	−0.33 ± 1.28	−1.02 ± 1.10	0.03

Abbreviations: BNT = Boston Naming Test; FH = family history; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised.
[a]Values are mean ± SD. Results from *t* test with Bonferroni correction.

therapy.[22] In contrast to a previous study,[23] the incidence of IPI in the negative-FH group (51%) was higher than in positive-FH group (25%), which may be a result of the sample size and or the inclusion of heterogeneous patients in our positive-FH group. Despite these differences, our results are consistent with a previous study that showed similar surgical outcome[24] for both sporadic and familial cases and the occurrence of IPI in FMLTE that varied from 10% to 35%.[2] We also observed a more severe AI of hippocampi in the negative-FH group, suggesting that different mechanisms may be involved in the development of hippocampal sclerosis in the positive-FH group.[2,13,23] So far, we are unable to explain the underlying mechanisms, but facing the complexity of hippocampal circuitry, we hypothesize that besides the influence of genetic background, the neuroplastic response to different insults (cellular loss, epileptic discharges, neuronal deafferentation) differs between the 2 groups.[23]

The neuropsychological profile was consistent with previous reports,[5,20] confirming memory impairment in both groups. We also observed that the positive-FH group had an average IQ range, but the IQ values in the negative-FH group were in the low average range, with significant differences between them ($p = 0.004$). Several studies have confirmed such intellectual impairment in both children[25] and adults[20] with MTLE, associating it with the early onset of seizures, the duration of active epilepsy, AED polytherapy, and a high seizure frequency.[22,25,26] Because the 2 groups were equivalent with regard to all

Figure Voxel-based morphometry comparing patients with negative and positive family history



Statistical maps of areas with more gray matter atrophy in the group with a negative family history of epilepsy compared with the group with a positive family history are overlaid on a multislice display of coronal images of a smoothed T1 template. The respective *T* value bar is shown in red.

these characteristics, we believe that the genetic background (i.e., the presence of an FH of epilepsy) as well as the lower educational level may play a role in the complex results on IQ performance. It is less probable that the generalized neuropsychological effects of MTLE are exclusively attributable to HA; instead, these may reflect the widespread harmful neurobiologic effects caused by recurrent seizures or by the IPIs.[20] In support of this concept, our results from whole brain VBM analysis demonstrated a bilateral, widespread pattern of preoperative GMA and WMA in the group with a low average IQ (negative FH), contrasting with a more restricted pattern in the positive-FH group. It is conceivable that, to some extent, the worse performance of the negative-FH group might be related to the widespread brain injury revealed by morphometry, which may be related to more frequent initial, and perhaps more intense, IPIs in these patients.

Unfortunately, we do not have data on the IQ performance of these patients with refractory disease during childhood or adolescence, which could be used to exclude a progressive cognitive decline throughout their lives.[27] Further prospective studies comparing the cognitive performance of patients with a positive and negative FH of epilepsy remain necessary to elucidate whether these 2 groups have a different progression of cognitive impairment.

In addition, the negative-FH group performed less well on the BNT and delayed recall tests. We have been unable to identify studies comparing the neuropsychological performance of MTLE patients with and without an FH of epilepsy, but we can hypothesize that the differences we found may be related in part to the more severe HA in the negative-FH group.[28,29] The hippocampus is a central component of the medial temporal lobe memory system, and its structural integrity is necessary for declarative memory, mainly episodic memory, as measured by the WMS-R delayed recall test.[30] Recently, the hippocampus has also been associated with semantic processes (such as naming pictures in BNT) as demonstrated by strong correlations between hippocampus GM density and a confrontation-naming test in patients with Alzheimer disease.[29] Moreover, we showed in a previous study that the volume of the left hippocampus was a significant and independent predictor of verbal memory and BNT performance in patients with MTLE.[5] Thus, HA most likely contributes to the reduction in retrieval efficiency in patients with refractory MTLE.[31]

We identified a restricted pattern of GMA/WMA in the positive-FH group and a widespread distribution in the negative-FH group. The bilateral, extratemporal extent of GMA and WMA in patients with refractory MTLE has been described previously with VBM and diffusion tensor imaging analyses,[4,32] but there have been no comparisons between patients with and without an FH of epilepsy. The reasons why the 2 groups presented different patterns of GMA remain unclear, but we can hypothesize that in the positive-FH group the development of HA is determined by much stronger genetic predisposition, such that for some patients, the genetic effects may be strong enough to induce HA and MTLE with the minimal influence of environmental factors.[33] It is probable that in the negative-FH group, hippocampal sclerosis results from a complex interaction of stronger environmental factors (brain infection, trauma, etc.).[34] In agreement with this hypothesis, a previous study revealed a more pronounced mossy fiber sprouting in the fascia dentate of a sporadic MTLE group, suggesting that patients with FMTLE respond differently to plastic changes induced by cellular loss, neuronal deafferentation, or recurrent seizures.[23] Accordingly, it is possible that recurrent "brain insults" are required for the development of HA, with simultaneous involvement of different brain regions; this would lead to a widespread bilateral pattern of damage, including thalami. However, we cannot exclude the possibility that recurrent seizures have different effects within and outside the limbic system of positive-FH and negative-FH groups,[35,36] because bilateral thalami atrophy in the negative-FH group may result from more severe and widespread injury. Despite the limitations of using T1 images to investigate WM abnormalities,[16,37] 1 previous study with VBM[4] showed temporal and extratemporal WMA in refractory MTLE. The underlying mechanisms for these abnormalities are still unclear and may involve different factors, such as myelin dysfunction and demyelination,[38] as well as microdysgenesis.[39] These results suggest that chronic refractory MTLE is associated with WM abnormalities, regardless of its genetic or sporadic aspect. Therefore, we can hypothesize that these chronic abnormalities in WM are possibly related to the cognitive dysfunction observed in patients with MTLE.[40]

We believe that the lower IQ performance in the negative-FH group is somehow related to the more widespread pattern of GMA and WMA, because we did not identify anatomically localized results from correlations between GM maps and individual neuropsychological scores. This is in accordance with a previous study[17] that showed correlations between GM loss and cognitive dysfunction at a global level in patients with left MTLE, but without anatomically localized results, suggesting that IQ performance is subserved by a widespread network, rather than an anatomically localized region. This finding

supports our hypothesis that the IQ performance in the negative-FH group is probably related to the widespread pattern of structural abnormalities in comparison with the positive-FH group.

Our results show that refractory patients with negative FH are more likely to develop more severe neuropsychological deficits, HA, and widespread extrahippocampal damage, compared with patients with positive FH. Patients with negative FH have more frequent and stronger deleterious environmental factors, which may influence the extensive structural damage and cognitive deficits. By contrast, patients with positive FH present less severe neuropsychological deficits and more restricted structural abnormalities. In patients with a positive FH, hippocampal sclerosis may develop under stronger genetic influence and less influence of environmental factors. Further studies remain necessary to elucidate how these abnormalities progress when seizures remain refractory.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Drs. Clarissa Lin Yasuda and Fernando Cendes.

DISCLOSURE

Dr. Yasuda reports no disclosures. Dr. Morita has received research support from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP). Dr. Alessio reports no disclosures. Ms. Pereira has received research support from FAPESP. Dr. Balthazar reports no disclosures. Mr. Saúde receives research support from Fapemig/Finep and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). Dr. A.L.F. Costa, Dr. A.L.C. Costa, Dr. Cardoso, and Dr. Betting report no disclosures. Dr. Guerreiro serves on scientific advisory boards for and/or has received funding for travel from Novartis, Janssen-Cilag, and GlaxoSmithKline; and serves as an Associate Editor of *Arquivos de Neuro-Psiquiatria*. Dr. Damasceno reports no disclosures. Dr. Lopes-Cendes serves as Section Editor for the *Brazilian Journal of Medicine and Biological Research*; and receives research support from FAPESP and CNPq. Dr. Tedeschi and Dr. de Oliveira report no disclosures. Dr. Cendes receives research support from FAPESP and CNPq.

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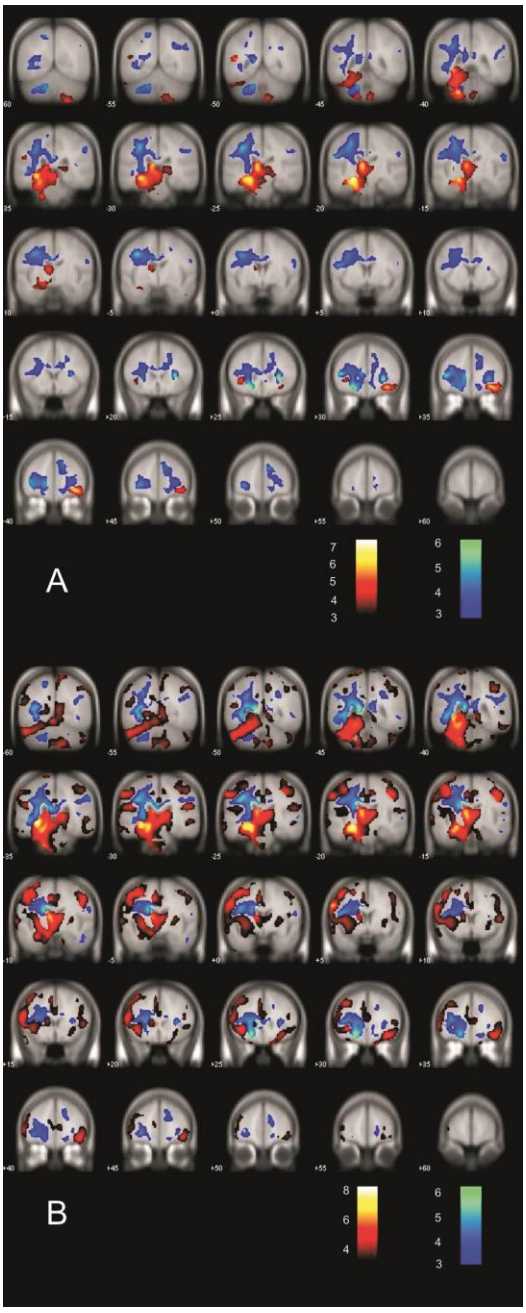

Figure e-1. Areas with GM and WM atrophy in the *positive-FH* (A) and *negative-FH* (B) groups. Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template. Each group has two maps: GM (red bar) and WM (blue bar), with their respective T-value bar.

Table e-1. Results from whole brain parametric analyses, areas with GM atrophy on *positive-FH*.

Hemisphere. anatomical location	Voxel wise				MNIcoordinates
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left. Hippocampus, amygdala, parahippocampal gyrus, thalamus;	52923	<0.0001	7.49	6.7	-22 -20 -12
		<0.0001	6.57	6	-30 -36 -6
		<0.0001	6.33	5.82	-28 -28 -12
		<0.0001	6.11	5.64	35 32 -11
2. Left. Inferior frontal gyrus, insula;	1353	<0.0001	5.09	4.81	-37 27 0
3. Left. Superior temporal gyrus, supramarginal gyrus;	725	<0.0001	5.28	4.96	-47 -50 15
4. Left. Insula. inferior parietal lobule;	254	0.002	4.05	3.89	-52 -34 24
5. Left. Cuneus. middle occipital gyrus,	131	0.001	4.38	4.19	-8 -102 3
6. Right. Cerebellum;	6504	<0.0001	5.02	4.74	23 -63 -58
		0.001	4.37	4.18	6 -46 -52
		0.002	4.11	3.95	15 -55 -51
7. Right. Inferior frontal gyrus, middle frontal gyrus;	6043	<0.0001	6.33	5.82	36 40 -9
8. Right. Lingual gyrus;	404	0.002	3.99	3.85	19 -90 -7

Results reported on a Height threshold: T= 3, FDR (0.01), clusters > 100 voxels

Table e-2 . Results from whole brain parametric analyses. Areas with GM atrophy on *negative-FH*.

Hemisphere. anatomical location		Voxelwise			MNI coordinates
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left . Hippocampus, amygdala, uncus, parahippocampal gyrus, thalamus, caudate, insula, inferior temporal gyrus, inferior occipital gyrus, fusiform gyrus, transverse temporal gyrus, middle temporal gyrus, superior temporal gyrus, inferior frontal gyrus, cingulate gyrus, angular gyrus, superior parietal lobule, inferior parietal lobule, precentral gyrus, postcentral gyrus;	512887	<0.0001	8.49	7.29	-25 -20 -12
		<0.0001	8.42	7.24	-31 -35 -5
2. Right. Thalamus, insula, angular gyrus, precentral and postcentral gyri, angular gyrus, supramarginal gyrus;		<0.0001	7.6	6.69	-32 -27 -10
3. Left, Cerebellum;	5044	0.001	4.11	3.92	-33 -79 -48
		0.001	4.05	3.88	-41 -74 -49
		0.001	3.8	3.65	-25 -80 -50
4. Left, Postcentral gyrus, superior parietal lobule;	4064	<0.0001	4.41	4.2	-16 -44 75
		<0.0001	4.35	4.14	-14 -31 77
		0.002	3.51	3.4	-31 -46 70
5. Left, Middle temporal gyrus;	335	0.003	3.38	3.28	-51 2 -45
6. Left, Cuneus;	123	0.006	3.02	2.94	-13 -93 30
7. Right. Inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, Fusiform gyrus;	6262	<0.0001	4.16	3.98	54 -31 -2
		0.001	4	3.83	54 -39 -21

Results reported on a Height threshold: T= 3, FDR (0.01), clusters > 100 voxels

Table e-3. Results from whole brain parametric analyses, areas with more GM atrophy in *negative-FH* compared to *positive-FH*.

Hemisphere, anatomical location	Voxelwise				MNI coordinates
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left, Cingulate gyrus, inferior occipital gyrus, lingual gyrus, middle occipital gyrus, precuneus, cuneus, superior parietal lobule, paracentral lobule;	61441	0.049	4.17	3.9	-7 -39 31
		0.049	4.03	3.78	-8 -24 49
		0.049	3.84	3.62	-2 -26 31
2. Left, Precentral gyrus, middle frontal gyrus, postcentral gyrus, inferior frontal gyrus, superior temporal gyrus;	24693	0.049	4.2	3.93	-58 -15 25
		0.049	4.09	3.83	-37 33 46
		0.049	4.01	3.77	-64 -23 47
3. Left, Cerebellum, fusiform gyrus, middle occipital gyrus;	4708	0.049	3.41	3.26	-27 -88 -39
		0.049	3.33	3.18	-51 -69 -29
		0.049	3.17	3.04	-51 -69 -17
4. Left, Middle temporal gyrus, superior occipital gyrus, middle occipital gyrus, angular gyrus;	1464	0.049	3.8	3.59	-37 -78 17
		0.049	3.23	3.1	-32 -77 27
5. Left, Inferior temporal gyrus, middle occipital gyrus, middle temporal gyrus;	879	0.049	3.7	3.5	-47 -63 -2
	767	0.049	3.86	3.64	-9 -37 78
6. Left, Cingulate gyrus;	520	0.049	3.16	3.03	-7 25 14
	484	0.049	3.33	3.18	-35 -42 41
	266	0.049	3.06	2.94	-71 -42 -8
		0.049	2.86	2.77	-69 -39 -20
	257	0.049	3.9	3.68	-6 -30 -54
7. Left, Cerebellum;	124	0.049	2.88	2.78	-16 -39 -32
8. Right, Cingulate gyrus, inferior frontal gyrus, thalamus, lentiform nucleus, caudate;	19755	0.049	3.9	3.67	10 3 5
		0.049	3.72	3.52	5 -4 2
		0.049	3.55	3.37	9 12 -29
9. Right, Transverse temporal gyrus, insula,	18881	0.049	4.66	4.31	35 -17 46

superior temporal gyrus, precentral gyrus, inferior parietal lobule, postcentral gyrus;					
		0.049	4.4	4.09	44 -18 34
		0.049	3.59	3.41	43 -33 19
10. Right, Inferior occipital gyrus, fusiform gyrus, lingual gyrus, middle occipital gyrus, cuneus;	7585	0.049	4.54	4.2	39 -93 -11
		0.049	4.19	3.92	12 -100 -13
		0.049	4.09	3.83	42 -76 -5
11. Right, Cerebellum;	4677	0.049	3.46	3.3	35 -36 -37
		0.049	3.34	3.2	20 -32 -35
		0.049	3.34	3.19	49 -44 -34
12. Right, Inferior frontal gyrus, middle frontal gyrus;	1280	0.049	3.08	2.96	44 33 25
		0.049	3.02	2.9	41 42 20
13. Right, Middle temporal gyrus, superior temporal gyrus;	1124	0.049	3.23	3.1	57 -35 -3
14. Right, Angular gyrus, inferior parietal lobule;	1103	0.049	3.61	3.43	49 -72 42
15. Right, Extra-nuclear, thalamus;	597	0.049	3.2	3.07	3 -32 7
	308	0.049	3.36	3.21	18 -48 76
16. Right, Middle frontal gyrus, superior frontal gyrus;	238	0.049	3.19	3.06	28 50 10

Results reported on a Height threshold: T= 3, no FDR, clusters > 100 voxels

Table e-4. Results from whole brain parametric analyses, areas with WM atrophy on *positive-FH*.

Hemisphere, anatomical location		Voxelwise			MNI coordinates
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left, Sub-gyral, cingulated gyrus, precentral gyrus, inferior and midle frontal gyri, inferior occipital gyrus, insula, lingual gyrus, middle occipital gyrus, middle temporal gyrus, supramarginal gyrus, angular gyrus, cuneus;	181240	<0,0001	6,27	5,77	-23 26 -11
		<0.0001	6.26	5.76	29 24 5
		<0.0001	5.78	5.38	-44 32 10
2. Left, Cerebellum;	9610	<0.0001	5.61	5.23	-12 -68 -38
		<0.0001	5.17	4.87	-26 -67 -34
		<0.0001	4.87	4.62	-15 -46 -31
3. Right, Supramarginal gyrus, angular gyrus;	2706	<0.0001	4.36	4.17	51 -56 37
		0.001	3.96	3.82	31 -54 36
4. Right, Transverse temporal gyrus, insula, superior temporal gyrus, precentral gyrus, postcentral gyrus, supramarginal gyrus, inferior parietal lobule;	6552	<0.0001	4.29	4.11	57 -15 26
		<0.0001	4.28	4.1	55 -33 40
		0.001	4.19	4.02	58 -39 32
5. Right, Middle frontal gyrus, cingulate gyrus;	566	0.003	3.21	3.13	22 -6 47
6. Right, Cingulate gyrus, precuneus;	258	0.003	3.33	3.24	11 -51 36
7. Right,Fusiform gyrus, inferior temporal gyrus;	113	0.003	3.23	3.14	50 -4 -30

Results reported on a Height threshold: T= 3, FDR (0.01), clusters > 100 voxels

Table e-5. Results from whole brain parametric analyses, areas with WM atrophy on *negative-FH*

Hemisphere, anatomical location	Voxelwise				MNI coordinates
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left, Sub-gyral, insula, transverse temporal gyrus, inferior temporal gyrus, middle occipital gyrus, superior temporal gyrus, middle temporal gyrus, cuneus, supramarginal gyrus, cingulate gyrus, middle frontal gyrus, postcentral gyrus, inferior frontal gyrus, precentral gyrus;	182687	<0.0001	6.28	5.73	-14 -47 12
		<0.0001	6.15	5.63	-20 29 -12
		<0.0001	6.09	5.58	-26 -81 9
2. Left, Cerebellum;	5926	<0.0001	4.74	4.48	-13 -69 -32
3. Left, Sub gyral, fusiform gyrus, inferior temporal gyrus, middle temporal gyrus;	1271	0.001	3.58	3.46	55 -14 -20
4. Right, Precentral gyrus, postcentral gyrus;	2038	0.001	3.65	3.52	59 -12 26
		0.001	3.58	3.46	56 1 16
		0.006	2.97	2.9	56 -3 25
5. Right, Sub-gyral, inferior temporal gyrus, middle occipital gyrus;	1247	0.001	3.8	3.66	43 -63 -4
		0.001	3.56	3.44	37 -66 2
		0.007	2.88	2.82	49 -57 -6
6. Right, Middle temporal gyrus, superior temporal gyrus;	639	<0.0001	4.48	4.26	54 -49 1
7. Right, Cerebellum;	293	0.001	3.59	3.47	23 -65 -33
		0.001	3.57	3.45	47 -10 -33
8. Right, Superior temporal gyrus;	276	<0.0001	4.86	4.58	63 -24 6
9. Right, Precuneus;	139	0.005	3.04	2.96	16 -57 54
10. Right, Sub-gyral, precentral gyrus;	110	0.007	2.89	2.82	35 -5 36

Results reported on a Height threshold: T= 3, FDR (0.01), clusters > 100 voxels

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Quantitative MRI techniques in MTLE: Toward a better understanding of hippocampal sclerosis

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The histologic hallmarks of hippocampal sclerosis (HS) are cell loss and gliosis of the hippocampus (Thom, 2008; Blumcke et al., 2009). The neuronal damage often involves also the amygdala, uncus, and parahippocampal gyrus (Gloor, 1991). HS has been recognized as the most commonly encountered pathologic substrate of mesial temporal lobe epilepsy (MTLE).

Several imaging modalities are useful for identifying in vivo signs of HS. Imaging analysis can be qualitative and quantitative.

Qualitative MRI Techniques

Images should be acquired with a specific epilepsy protocol that should include thin coronal slices. T_2-Weighted or fluid attenuated inversion recovery (FLAIR) images are important to assess qualitatively the signal intensity.

The majority of patients with HS undergoing presurgical evaluation will have a clear-cut unilateral atrophic hippocampus with increased T_2-weighted signal and a normal-appearing contralateral hippocampus (Fig. 1). However, the visual binary paradigm breaks down in the presence of symmetric bilateral disease or mild unilateral disease.

Quantitative MRI Techniques in MTLE: Towards a Better Understanding of HS

It is still unclear why, when, and how neuronal damage and dysfunction occur in patients with MTLE. It is possible, for example, that not all types of seizures do cause harm, or yet, that some individuals are more resistant to seizure-induced damage than others. Genetic background, age, and type of initial brain insult, and other environmental factors, most likely interact in a number of ways, making it difficult to determine the exact mechanisms of ongoing brain damage in TLE (Cendes, 2005). In addition, seizure-related damage may be expressed in a number of ways, and not necessarily represent neuronal loss or atrophy (Sutula, 2004). For example, many patients with TLE who do not respond well to treatment have progressive memory loss and signs of diffuse cognitive impairment, as well as progressive increase of bilateral epileptiform discharges (Morrell, 1989).

Retrospective studies have shown a significant relationship between a history of prolonged febrile seizures (FS) in early childhood and HS (Cendes, 2005). However, population studies have shown different results (Camfield et al., 1994). The interpretation of these observations remains controversial. One possibility is that the early FS damages the hippocampus and are, therefore, a cause of HS. Another possibility is that the child has prolonged FS because the hippocampus was previously damaged due to a prenatal or perinatal insult or to a genetic predisposition. In either hypothesis, however, a cross-sectional, retrospective analysis would result in a positive correlation between seizure frequency and degree of HS, thus not solving the enigma of cause or consequence. Interestingly, Falconer and Taylor in 1968, developed the concept that HS is both a cause as well a consequence of epileptic seizures, which has been supported by more recent investigations (Cendes, 2005; Blumcke et al., 2009).

There is a strong correlation between HS and the severity of the epilepsy in series of surgical patients (Semah et al., 1998). However, the findings of magnetic resonance imaging (MRI) abnormalities in patients with good outcome or seizure remission (Cardoso et al., 2006), indicates that HS is found not only in patients with medically refractory TLE (Kobayashi et al., 2001, 2002).

There are several techniques to quantify MRI changes in patients with MTLE including: manual, semiautomatic, or automatic volume measurements of hippocampi and other structures. Structural MR images can also be coregistered with other imaging modali
emission tomography (PET) and si
computed tomography (SPECT), a
tional information.

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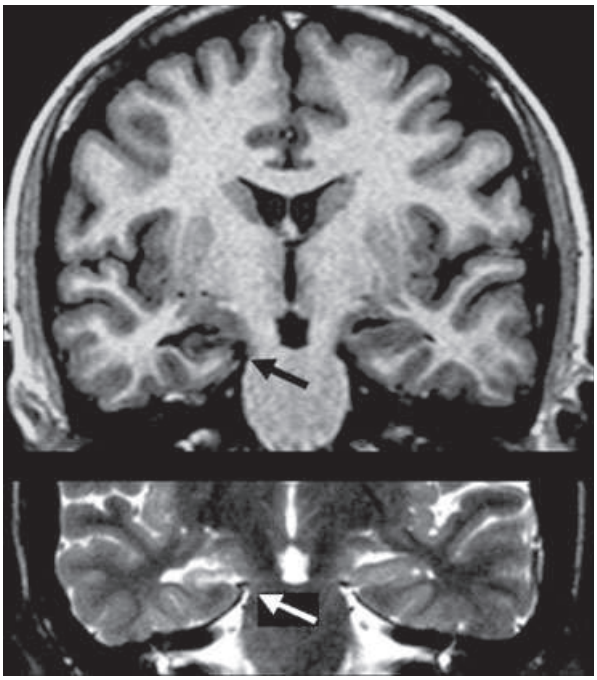

Figure 1.
Coronal T_1-weighted inversion recovery image (top) and T_2-weighted fast spin echo (FSE) image (bottom) from a patient with right mesial temporal lobe epilepsy (MTLE) showing classic features of hippocampal sclerosis on the right side: atrophy, loss of internal structure, and hyperintense signal on T_2-weighted image. *Epilepsia* © ILAE

Here are some examples of how quantitative MRI analysis may help toward a better understanding of HS.

MRI volumetric studies

MRI-based volumetric studies generate numerical data that permit better comparisons of the degree of medial temporal atrophy in various subgroups of patients. The findings can be statistically correlated with various clinical parameters and thereby lead to better discrimination and understanding of the underlying condition.

Several cross-sectional MRI studies have shown an association between the severity of atrophy of the hippocampus and other mesial temporal structures with the duration of epilepsy and seizure frequency (Kalviainen & Salmenpera, 2002; Theodore et al., 2003). Cross-sectional MRI studies, however, have limitations for identifying the cause of atrophy: the initial precipitating insult; underlying pathology; chronic progression of damage caused by the initial insult that may be independent of recurrent seizures; or direct consequence of seizures. Another problem is the inaccurate quantification of seizure frequency. Longitudinal studies may overcome several of these limitations (Liu et al., 2002; Fuerst et al., 2003).

Patients with MTLE have significant reduction of the volume of the cortical structures with close anatomic and functional connections to the hippocampus—that is, the entorhinal and perirhinal cortices (Bernasconi et al., 2003; Bonilha et al., 2003b). Other structures, such as the parahippocampal and temporopolar cortices, seem to be less affected (Bonilha et al., 2003b).

Studies in familial mesial temporal lobe epilepsy (FMTLE) showed that MRI signs of HS were present in affected individuals (Kobayashi et al., 2001) and in asymptomatic family members (Kobayashi et al., 2002). In fact, two of the asymptomatic individuals in whom we documented hippocampal atrophy developed MTLE a few years after they had MRI. These findings support the view that genetically determined mechanisms might play an important role in the development of hippocampal damage, which may be hereditary, at least in the context of FMTLE (Kobayashi et al., 2001, 2002).

Measurements of hippocampal signal

Studies with T_2-signal quantification (relaxometry) showed a high sensitivity and specificity for hippocampal signal abnormalities in patients with TLE (Van Paesschen et al., 1997; Briellmann et al., 2002). T_2-signal abnormalities appear to correlate with gliosis and may not be directly related to the degree of neuronal loss (Van Paesschen et al., 1997; Briellmann et al., 2002).

Hippocampal texture analysis

Texture analysis of MR images is a quantitative method that can be used to detect and quantify structural abnormalities in different tissues. It makes it possible to assess the degree of gray-tone modifications, which are thought to correspond to underlying functional and anatomical changes (Antel et al., 2003). In this setting, texture analysis may be sensitive to detect subtle changes in MRI and to extract more information than visual assessment. In fact, previous studies have shown texture hippocampal abnormalities in MTLE patients, including in the side contralateral to the HS (Yu et al., 2001; Bonilha et al., 2003a).

Voxel-based morphometry

Voxel-based morphometry (VBM) permits a voxel by voxel comparison between different groups of three-dimensional MRIs, thereby allowing fully automated statistical comparisons of the concentration (or relative volume) of gray matter, white matter, or cerebrospinal fluid (Good et al., 2001). Images undergo a series of preprocessing steps in order to correct for some gross differences in shape and volume of brain, in an attempt to preserve its quantity while ensuring a good spatial alignment between patients and controls (Good et al., 2001).

Recent studies have shown that in patients with MTLE the reduction in gray matter concentration (GMC) extends beyond the hippocampus ipsilateral to the seizure origin,

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involving cortical and subcortical structures connected to the hippocampus and parahippocampal region, thus confirming the findings of conventional manual volumetry (Bernasconi et al., 2004; Bonilha et al., 2004).

VBM analyses on MTLE patients who underwent surgery showed different patterns of preoperative GM atrophy between the seizure-free group and the failure group. In addition, there was a postoperative significant relative increase of white matter and GM in the seizure-free group, but not in those who continued with seizure, suggesting that successful surgery may offer better chances of favorable brain plasticity in patients with MTLE (Yasuda et al., 2008).

Proton magnetic resonance spectroscopy studies in TLE

Proton magnetic resonance spectroscopy (MRS) studies have shown focal reductions of *N*-acetyl aspartate (NAA) signal in patients with different forms of TLE, including those with normal MRI (Cendes et al., 2002).

In surgically treated MTLE-HS the usual mesial temporal abnormalities are decreased NAA ipsilateral to the sclerotic hippocampus (in >90%), and also in the contralateral hippocampus (in 30–40%) (Cendes et al., 2002).

Interestingly, upon successful resection of a sclerotic hippocampus, the contralateral mesial temporal NAA abnormality often resolves within several months after seizure control (Hugg et al., 1996; Serles et al., 2001).

Conclusions

Modern neuroimaging techniques—including high-resolution structural MRI, MRS, and other functional imaging modalities—have provided substantial new insights suggesting that epileptogenic damage is both a cause and a consequence of repeated seizures. However, the causes of MTS and mechanisms of progression of damage are still unknown. Recognition of the syndrome of familial MTLE indicates a strong genetic role as one of the probable causes for the development of MTS.

Disclosure

None of the authors has any conflict of interest to disclose.

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Imaging Characterization of Familial Temporal Lobe Epilepsies

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Introduction

Mesial Temporal Lobe Epilepsy

Structural correlates of MTLE include hippocampal sclerosis (HS), glial tumors, vascular malformations, and neurodevelopmental lesions. Gliotic lesions due to trauma or infections can also give rise to MTLE. HS is the major neuropathological substrate in patients with MTLE, and it is present in 60–70% of patients with MTLE who undergo surgery for treatment of medically refractory seizures. HS most likely has different causes in different individuals, and may result from complex interactions among genetic and environmental factors. Histopathological hallmarks include segmental loss of pyramidal neurons, granule cell dispersion, reactive gliosis, and axonal sprouting of surviving neurons. The mechanisms underlying the development of MTLE remain undetermined. It has been hypothesized that developmental malformations or precipitating events in early development, such as febrile seizures, may initiate a lasting and progressive change that leads to a propensity of the hippocampus to generate seizures in later life. Animal models of febrile seizures suggest that, indeed, early life seizures cause lasting changes in the excitability of hippocampal neurons.

The hallmarks of MTLE are typical limbic seizures with or without loss of consciousness. The first recurring seizures usually occur in late childhood or early adolescence. The most common initial ictal symptom is a visceral sensation, described usually as rising epigastric sensation (also refereed to as epigastric aura) that may be followed or accompanied by other features including emotional disturbances such as fear, autonomic symptoms, and olfactory or gustatory sensations. Auras typically occur in isolation and can precede seizures with impairment of consciousness (complex partial seizures). The latter commonly begin with a motionless stare and oroalimentary automatisms (e.g., lip smacking, chewing), during which the patient may be unresponsive. Gestural and reactive automatisms of the limbs or sometimes the whole body are also common. Dystonia of one extremity is usually contralateral to the side of ictal onset. Seizures typically last 1–2 min.

The neurological examination is usually normal. Most atients have deficits in episodic memory. Verbal memory is mostly affected with left MTLE, whereas visuospatial memory is more affected with right MTLE. The interictal electroencephalogram (EEG) of patients with MTLE typically shows unilateral or bilateral independent mesial temporal spikes, best seen with basal (sphenoidal, inferior temporal) derivations. Ictal EEG patterns commonly consist of rhythmic 5–7-Hz discharges seen in the mesial temporal region on the side of onset. High-resolution MRI often demonstrates unilateral and sometimes bilateral hippocampal atrophy associated with hyperintense T2 signal in one or both hippocampi, which is highly specific for HS. More detailed high resolution MRI analyses reveal a network of gray matter atrophy that involves mesial temporal and other structures interconnected with the limbic system, including amygdala, entorhinal, perirhinal, and parahippocampal cortices, and thalamus. Most patients are sporadic, but familial aggregation also occurs.

Familial Temporal Lobe Epilepsy

Familial MTLE

The best definition of familial MTLE is based on the familial recurrence of MTLE in the absence of any suggestion of other partial (including lateral TLE symptoms) or generalized epilepsy syndromes in other affected family members. The finding of at least two MTLE patients in one family is suggestive of familial MTLE. The observation of an autosomal dominant inheritance pattern with incomplete penetrance implies the presence of asymptomatic carriers of the genetic abnormalities, who can transmit the disease to their offspring. Therefore, we should consider inclusion of not only families with affected first-degree relatives, but also those with affected second and third degree relatives. This criterion has not been employed in some reported series, leading to exclusion of many possible familial MTLE kindreds.

Most affected individuals with familial MTLE have a benign clinical course, and in some families all affected members have good seizure control or remit after a short period of seizures. However, as in patients with nonfamilial MTLE, some affected family members may have poor seizure control and require surgical treatment. Although magnetic resonance imaging (MRI) signs of hippocampal sclerosis, including hippocampal atrophy (HA) and hyperintense T2 signal, are more frequent and more pronounced in patients with refractory seizures, these changes are also observed in patients with good clinical outcome, and even in asymptomatic family members. These are strong indicators that genetic factors play a role in the genesis of hippocampal pathology in patients with familial MTLE. While the pattern of inheritance is autosomal dominant with incomplete penetrance, the genetic background in familial MTLE does not imply a more widespread structural abnormality on MRI.

Familial TLE with auditory auras

Familial TLE with auditory auras (also described as autosomal dominant partial epilepsy with auditory features (ADPEAF)) is a benign epilepsy syndrome, characterized by auras described as buzzing, roaring, radio or motor like sounds, distortions in sounds and words. Although other manifestations such as psychic, cephalic, and other sensory and motor phenomena can occur, the auditory auras are a hallmark of this syndrome. Sometimes ictal aphasia and visual misperceptions can occur and, in some families, secondarily generalized tonic–clonic seizures (GTCS) are frequent before treatment. The EEG may show posterior temporal epileptiform discharges, but is frequently normal.

The pattern of inheritance observed is autosomal dominant with incomplete penetrance. Molecular studies identified linkage to chromosome 10q, and mutations in the *leucine-rich, glioma-inactivated 1* gene *(LGI-1)* have been identified. However, only 50% of families presenting the typical phenotype have LGI-1 mutations suggesting genetic heterogeneity.

Age of onset is variable, usually in the second or third decade of life, and seizures are easily controlled by AEDs. No signs of HA or HS-related signal changes on MRI have been described in different series: however, we have found subtle abnormalities in the neocortical aspects of the temporal lobes.

The prevalence and incidence of these two forms of familial TLE are unknown. However, familial MTLE is apparently more common than familial TLE with auditory auras. There is no predominance in any particular ethnic group, and families with MTLE and with TLE with auditory auras have been described in several countries. There is probably an underestimation of the real prevalence of both forms of familial TLE worldwide, especially in families with predominantly good outcomes.

Ascertainment of these families requires detailed questioning of patients and family members, a practice that has only been emphasized recently, as MTLE, as well as other partial epilepsies, has generally been considered to be symptomatic and largely due to environmental factors.

There is no evidence to suggest that familial partial epilepsy with variable foci, partial epilepsy with auditory features, or temporal lobe variants of benign childhood epilepsy with centrotemporal spikes ever evolve into MTLE with HS. This observation suggests a clear distinction between familial MTLE and these other familial epilepsy syndromes.

Background

Neuroimaging in Familial MTLE

MRI evaluation in familial MTLE has shown a high frequency of HA and other signs of HS (**Figure 1**), even in individuals with seizure remission and asymptomatic family members (**Figure 2**). The identification of MRI signs of HS in familial MTLE patients with a benign clinical course supports the view that the presence of HA is not always associated with refractory epilepsy. Available data indicate that MRI abnormalities, determined by visual analyses, are similar in familial and sporadic MTLE with HS.

Patients with intractable familial MTLE present a clinical profile and most histological findings comparable to patients with sporadic MTLE. Interestingly, mossy fiber sprouting may be more pronounced in patients with sporadic MTLE. This finding suggests that, when compared with sporadic MTLE, patients with familial MTLE may respond differently (i.e., display different plastic changes) to cell loss, neuronal deafferentation or epileptic seizures. This finding is in keeping with our recent MRI studies with voxel-based morphometry

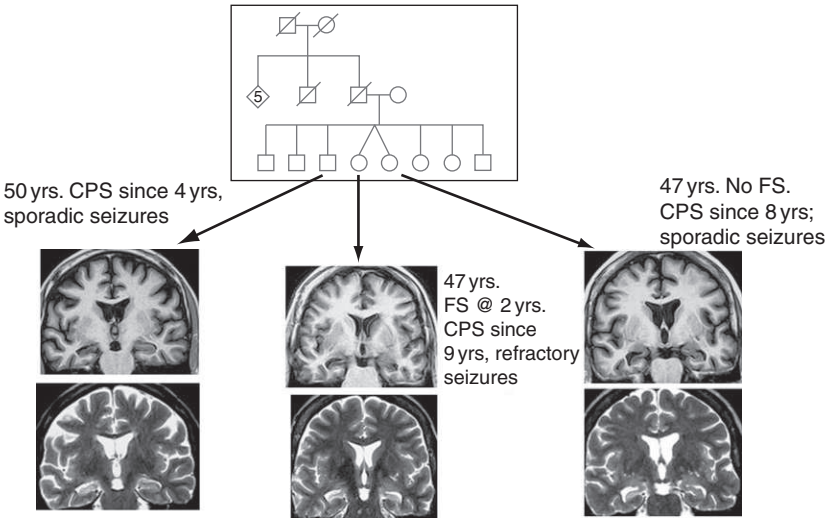

Figure 1 Reduced pedigree from one family with familial MTLE, showing coronal T1 and T2 MRIs showing signs of hippocampal sclerosis: atrophy, hyperintense T2 signal, abnormal shape and abnormal internal structure of right hippocampus in three sibs. CPS: complex partial seizures; FS: febrile seizures.

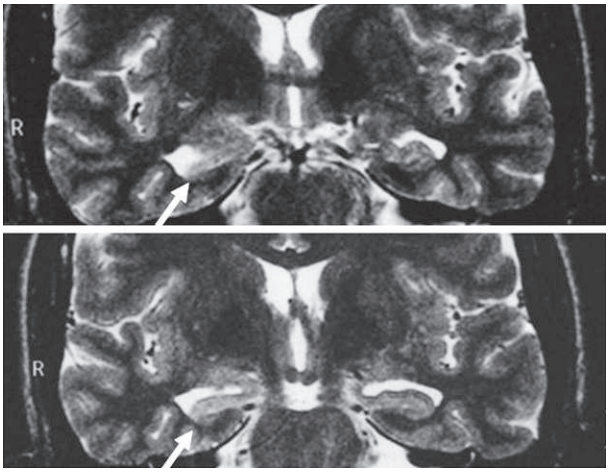

Figure 2 Coronal T2-weighted MR images in a 39 years old man from a family with MTLE. He had his first seizure at 17 years of age and a few other seizures during life. He has been seizure free without medication for several years. Observe the right hippocampal atrophy with hyperintense T2 signal and abnormal shape (arrows).

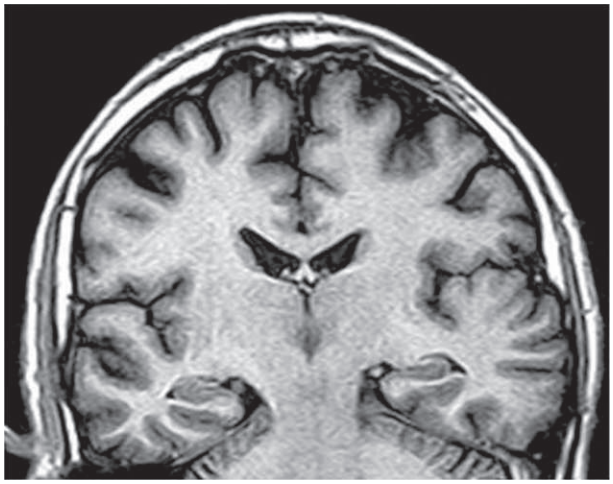

Figure 3 Coronal T1-invertion recovery MRI showing enlargement of left temporal lobe in a patient with familial TLE with auditory auras. Observe also an abnormal pattern of the first and second temporal sulci as compared to the right side.

(VBM), demonstrating more widespread gray matter atrophy in patients with sporadic MTLE compared to familial MTLE as discussed below.

Neuroimaging in Familial TLE with auditory auras

No signs of HA are found on MRI studies, but we have observed a lateral temporal malformation pattern in 45% of affected individuals, including one asymptomatic carrier of the mutation. The left temporal lobes of these individuals seemed enlarged (Figure 3), and these patients sometimes show a protrusion of the brain parenchyma laterally, with an 'encephalocele-like' appearance. Anterior temporal lobe volumetry showed a significant global increase in only two individuals. The epileptogenic significance of these structural abnormalities is unknown.

Methods

Familial MTLE

Our group has performed a genome-wide scan with 332 microsatellite markers at ~12 cM intervals to identify the region harboring the main gene associated with HA

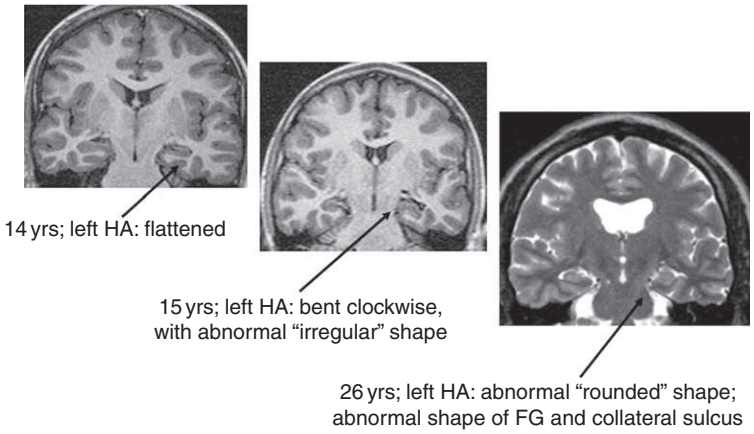

Figure 4 Coronal MRIs from asymptomatic family members of families with MTLE showing different patterns of hippocampal malformation (arrows). HA: hippocampal atrophy. FG: fusiform gyrus.

in a large kindred with familial MTLE. Additional 14 markers were genotyped in the candidate region. Two-point and multipoint LOD scores were calculated with the LINKAGE computer package. All genotyped individuals underwent MRI for evaluation of hippocampal abnormalities. Previous pedigree and complex segregation analysis provided evidence for the presence of a major gene predisposing to HA in familial MTLE.

In addition, we performed visual and volumetric analysis of all MRIs in 12 patients from this kindred who had seizures. Hippocampal measurements were made on 3 mm coronal T1-weighted images. Hippocampal malformation was defined according to previous publications (see Further Reading), and included hippocampi that were abnormally round, pyramidal in shape, with abnormal rotation or vertically orientated (**Figure 4**). All patients had clinical and EEG diagnosis of MTLE, except one patient who had had two generalized tonic–clonic seizures.

In a different study, we used an MRI automatic segmentation protocol and VBM to investigate 92 consecutive patients with benign MTLE (55 women and 37 men; mean age 42 years). Benign MTLE was defined as no disabling seizures reported by the patients, with only mild simple partial seizures occurring once a month or less. All patients and 40 controls (22 women, 18 men; mean age 32 years) were submitted to a 2T MRI scan. The volumetric 3D T1 *gradient echo* (GRE) sequence was used for the analysis. MRIs were normalized using linear and nonlinear transformations, and were automatically segmented using SPM5 (Wellcome Trust Centre for Neuroimaging, London, England; www.fil.ion.ucl.ac.uk) built-in routines. For VBM analysis, the images were smoothed further with an 8 mm Gaussian Kernel. Images were also normalized based on the total intracranial volumes of the controls. We compared differences between sporadic and familiar MTLE versus controls. For these comparisons, images were horizontally flipped according to the smaller hippocampus to avoid side to side cancellation. ANOVA was used, and a $p < 0.05$ false discovery rate correction was selected.

We also followed prospectively 64 individuals with familial MTLE from 28 families. Patients who fulfilled clinical criteria for MTLE (according to the ILAE classification scheme) were divided into three groups. (i) *Remission*: seizure-free for at least 2 years; (ii) *Benign*: less than six complex partial seizures (CPS)/year and no more than two secondary generalized tonic–clonic seizures per year; and (iii) *Refractory*: more than six partial seizures per year despite adequate antiepileptic drugs (AEDs). Thirty-five of these individuals had hippocampal volumetric measurements in two MRI scans, performed with a minimum of 1 year interval, which did not show progression of atrophy.

Familial TLE with Auditory Auras

We acquired MRIs in a 2T scanner (Elscint Prestige, Haifa, Israel) using a spoiled GRE sequence (TR = 22 ms, TE = 9 ms, flip angle = 35°, matrix = 256 × 220). These T1-weighted images were acquired with 1 mm isotropic voxels, and were subsequently transformed into ANALYZE format using MRIcro software (Chris Rorden, www.mricro.com). VBM analysis was performed using SPM99 (www.fil.ion.ucl.ac.uk). Images were then normalized to the standard space using 12 linear parameters and 7 × 8 × 7 nonlinear basis functions, using a brain mask. Spatially normalized images were resliced to an isotropic 1.5 mm and underwent segmentation of gray matter and modulation of the estimated concentration of tissue, based on the spatial deformations encountered during normalization. This technique preserves the quantity of gray matter and ensures a good spatial alignment between patients and controls. Finally, the images were convolved with an Isotropic Gaussian Kernel of 10 mm to minimize gyral interindividual variability. The resulting images were then compared using *t*-tests, to

determine differences in grey matter concentration (GMC) between controls and subjects with the LGI1 mutation from one large family. Contrasts were defined to estimate the probability of each voxel being gray matter. This analysis included grand mean scaling and proportional threshold masking (set to 0.8) and implicit masking. The results from the analysis are given in a parametric map of t-statistic (SPM(t)), and the SPM(t) is corrected for normal distribution (SPM(z)). Considering the previously observed subtle structural abnormalities in the temporal lobes of these same individuals, and the relative small number of participants, we examined clusters with at least 32 voxels that exceed $p < 0.01$, uncorrected threshold ($T = 2.39$). Group differences for age were assessed using one-way ANOVA, and the gender distribution was evaluated with χ^2 test.

Recent Results

Familial MTLE

We have identified linkage to chromosome 18p in a single family with MTLE. Multipoint and haplotype analysis localized the locus within a 13 cM interval. From the 12 patients in this family with seizures, one patient – who had had two generalized tonic–clonic seizures – did not have the haplotype, and MRI was normal. The remaining 11 patients with diagnosis of MTLE had MRI signs of hippocampal malformation, including hippocampal atrophy in 8 of them. All except one of these 11 patients had the haplotype. Further evaluation including asymptomatic family members would be helpful for clarifying the genetic basis of hippocampal malformation and hippocampal sclerosis in familial MTLE. However, our success in this linkage analysis provides clear evidence that HA may be caused by genetic factors, which can have major implications in the study of the pathophysiological mechanisms underlying MTS and its relationship with TLE.

For the MRI VBM study of benign MTLE, there were 52 patients in the sporadic MTLE group and 40 patients in the familial MTLE group. Our investigation evidenced a high frequency of structural abnormalities in patients with benign MTLE. VBM showed areas of gray matter atrophy that were more widespread in patients with sporadic TLE compared to familial MTLE (Figure 5), which

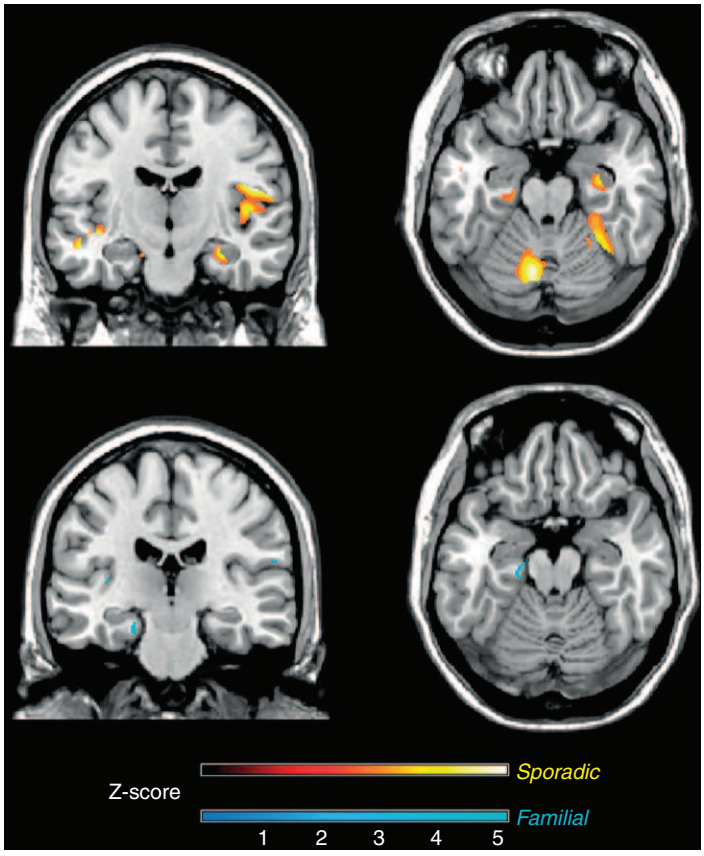

Figure 5 Results of the VBM comparisons among 40 patients with mesial temporal lobe epilepsy and positive family history (TLE, top row – hot colors), 52 patients with sporadic TLE (negative family history, bottom row – cold colors) and 40 controls showing areas of gray matter atrophy. The results are overlaid with an anatomical T1 template and displayed in two orthogonal planes (coronal and axial). The color bar in the inferior portion of the figure represents the number of standard deviations as compared to controls.

is in agreement with another study comparing postoperative histopathology studies in refractory sporadic and familial MTLE. Familial and sporadic TLE showed different patterns of atrophy, as observed in the VBM group comparisons. Multiple mechanisms involved in the pathogenesis of TLE are the probable explanation for this diversity. These findings indicate that environmental factors and modifier genes play an important role in the outcome of TLE.

We followed prospectively 64 individuals, from 28 families, with familial MTLE. Patients who fulfilled clinical criteria for MTLE were divided into three groups, as described above. Mean follow up was 93.4 ± 15.8 months (ranging from 45 to 121.9 months). At baseline they were divided as follows: benign – $n = 29$; remission – $n = 28$; and refractory – $n = 7$. At the last follow-up visit, 12 (41.4%) patients with benign FMTLE remained classified as benign, 6 (20.7%) became refractory, and 11 (37.9%) were in remission. In the subgroup of familial MTLE in remission, 21 (75%) remained without seizures; 6 (21.4%) were classified as benign familial MTLE, and one died (3.6%) from causes unrelated to epilepsy. All refractory patients remained refractory. Prospective follow-up of more than 7 years in patients with familial MTLE revealed that those with refractory seizures are unlikely to achieve seizure control with AEDs. In contrast, patients with benign familial MTLE for more than one year are likely to remit or remain under good seizure control. The majority of patients who had achieved seizure remission remained seizure-free and none became refractory.

Familial Temporal Lobe Epilepsy with Auditory Auras

Studies have reported no signs of HS in MRIs of patients from families with LGI-1 mutation. Enlargement and abnormal gyration, suggesting developmental abnormalities in the lateral cortex of the temporal lobe, were described in 53% of affected individuals in one family with LGI-1 mutation (**Figure 3**), a finding that requires confirmation. The MRI findings in that family are clearly distinct from the MRI findings in familial MTLE, and are consistent with the distinct seizure semiology in these two forms of familial TLE.

We performed a VBM study in 17 family members from a large kindred with familial TLE with auditory auras (three of them asymptomatic), all being carriers of the LGI1 mutation. We observed areas of increased GMC (compared to normal controls) in the left cerebellum, right parietooccipital region, and left hippocampus. In addition, these individuals presented with decreased GMC in the anterior portion of both temporal lobes, in the left precentral area, and in the right cerebellum.

The functional properties of the LGI1 gene remain unknown. This gene was cloned from the breakpoints of a glioblastoma cell line and its expression is reduced or absent in many high-grade gliomas. This evidence suggests a possible function related to cellular proliferation and/or tumor suppression. Furthermore, this gene is characterized by a central leucine-rich repeat region, which is involved in regulation of cell growth, adhesion, and migration. Therefore, LGI1 mutations could, possibly, be leading to subtle abnormalities of neuronal proliferation or migration that would result in dysgenetic lesions not easily detected by MRI.

Future Goals

Further structural and functional imaging and histopathological studies will shed light on the processes involved in genesis and progression of HS, and on other underlying mechanisms of sporadic and familial TLE epilepsies. The finding of a major gene mutation will be crucial for a better understanding of these functional and anatomic changes related to epileptogenesis in MTLE. The presence of structural brain abnormalities, e.g., in the form of GMC excess in patients with familial TLE with auditory auras, could be a consequence of the LGI-1 mutation and requires further investigation.

See also: **Classification**: Classification of Seizures and Syndromes; **Imaging**: Structural Imaging in Epilepsy; **Temporal Lobe Epilepsy**: Genetic Determinants of Temporal Lobe Epilepsy.

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Magnetic Resonance Imaging in Epilepsy Research: Recent and Upcoming Developments

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Introduction

Magnetic resonance imaging (MRI) of the brain has become an indispensable tool in the diagnosis and treatment of epilepsy patients. Since its introduction to the clinical routine in the early 1990s, the detection and characterization of epileptogenic lesions by MRI has improved substantially. This imaging progress has opened up the possibility of epilepsy surgery to more patients, and improved the prognosis for those who are finally undergoing surgery.

Major recent advances lie in the improvement of magnetic resonance (MR)-acquisition techniques, which include improvements in the scanner hardware (e.g., more powerful gradient systems and scanner magnets with increased field strengths) as well as the development of new MR sequences with better contrasts. Besides these developments, the postprocessing of structural MRI data has yielded increasingly insightful results in the detection of cortical and subcortical lesions. Finally, functional MRI (fMRI) has shown its powerful potential to predict postsurgical outcome or complications and to contribute to focus detection.

Developments in MR-Acquisition Techniques

High Field Strengths

During the early years of clinical MRI, the field strength used was rather low (<0.5 T). The majority of clinical magnets today are operated at a field strength of 1.5 T, but the improved signal-to-noise ratio (SNR) with stronger magnets (3 T and above), and the growing experiences with the pitfalls and problems of higher field strengths, have lead to a growing number of these stronger clinical magnets. The drawbacks of higher field strengths, such as increased radiofrequency-energy (applied to the patients) and larger field inhomogenieties and susceptibility artifacts, as well as differences in relaxation rates, have been overshadowed by the ability for faster imaging and/or increased resolutions. Although the use of 3-T magnets becomes more and more routine (at least in larger hospitals and special centers), even higher field strengths of 7 or 9.4 T are now constructed for use in patients by all the vendors. Although these high field-strength magnets are currently viewed rather critically (as were the first 3-T magnets when they were introduced), the increased SNR provided by this enhancement can be used for even more rapid imaging or increased resolution. Exemplary images show promising results (**Figure 1**), but the applicability of these magnets in routine clinical function is debatable – not only due to the much higher costs but also due to an increased ratio of side-effects (e.g., nausea or vertigo) experienced by initial subjects.

Multichannel Coils and Parallel Imaging

Besides the increase in field strength, the development of multichannel coils was one of the cornerstones that improved neuroimaging by enabling parallel data reconstruction, and thereby increasing SNR, allowing decreased scanning time and artifacts. The decrease in acquisition times (by a factor of 4 or even more) alleviates movement artifacts and reduces the influence of field inhomogenieties, which is especially important for fast echo planar imaging (EPI) acquisitions which are used for fMRI to measure the blood oxygen level dependent (BOLD) contrast and diffusion weighted imaging, and also provides higher resolution images (if the same

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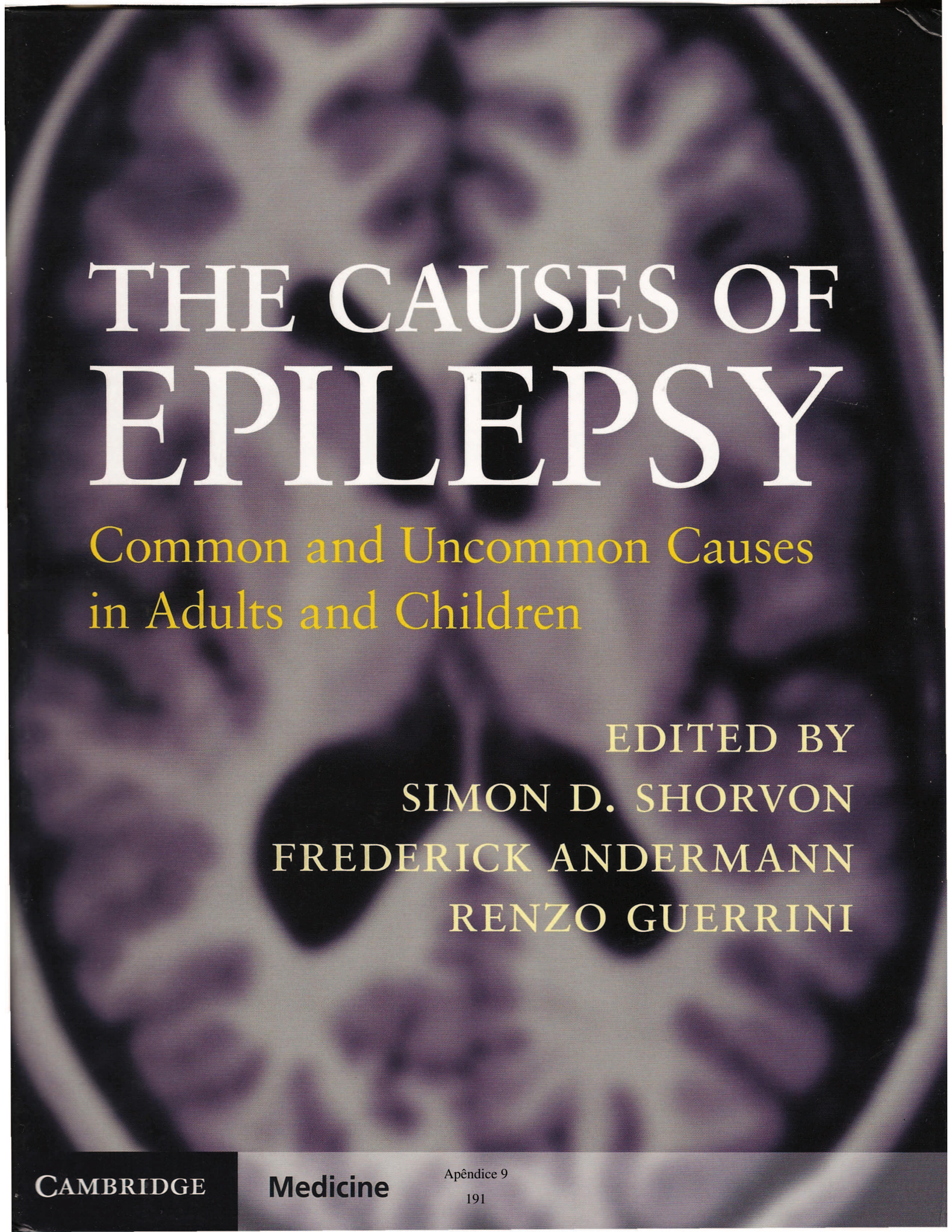
Apêndice 9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EPILEPSY
Common and Uncommon Causes
in Adults and Children
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Chapter 53

Hippocampal sclerosis

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The causal factors

Definitions

The terms "Ammon's horn sclerosis," "hippocampal sclerosis," and "mesial temporal sclerosis" are often used as synonymous. The term "sclerosis" is originally a macroscopic and descriptive one: it indicates shrinkage and induration of the structure. Hippocampal sclerosis (HS) is a histological term that indicates selective neuronal loss with secondary astroglial proliferation that affects various sectors of the hippocampus to a different degree: the most vulnerable to damage are the sectors cornu ammonis CA1, CA3, and endfolium (sector CA4), while the granule cells of the dentate gyrus, sector CA2, and subiculum are the most resistant (Fig. 53.1). The amygdala, uncus, and parahippocampal gyrus are often involved as well; thus, according to some authors, the term mesial temporal sclerosis would be more appropriate (Gloor 1997; Thom 2009). This cell loss, if sufficiently pronounced, will appear in magnetic resonance imaging (MRI) scans as a reduced volume or shrinkage of the hippocampus, often associated with changes in signal intensity. Therefore the MRI scan provides a marker for a known histopathological process (Van Paesschen *et al.* 1997) (Fig. 53.2).

Hippocampal sclerosis has been recognized as the most commonly encountered pathological substrate of mesial temporal lobe epilepsy (MTLE) (Wieser 2004). It is present in 60–70% of patients with MTLE who undergo surgery for treatment of medically refractory seizures (Falconer 1974). Other structural lesions can also cause temporal lobe epilepsy (TLE), such as hamartomas, glial tumors, vascular and congenital malformations, and gliotic lesions due to trauma or infections.

Epidemiology

Epilepsy affects approximately 1.0–2.0% of the population (Hauser *et al.* 1996). Epilepsies can be classified as generalized or localization-related (partial or focal) (ILAE 1989). Temporal lobe epilepsy is the most frequent form of partial epilepsy in adults (Hauser *et al.* 1996); however, the incidence of HS or MTLE in the general population is unknown, since most studies are based on surgical series. Nevertheless, HS contributes to a major part of partial seizures in adults which are often resistant to antiepileptic drugs. In one hospital-based study, half of patients seen in the epilepsy outpatient clinic had TLE, and half of these had MRI evidence of HS (Semah *et al.* 1998). In a recent series of 84 patients with well-controlled partial seizures, MRI volumetry showed hippocampal atrophy indicating mild HS in 39 (46%) patients (Cardoso *et al.* 2006). In surgical series, 60–70% of patients have HS (Babb and Brown 1987).

Pathogenesis of hippocampal sclerosis

Studies of the relationship between seizures and HS spans more than 150 years (Meencke 2009). The pathological condition was initially described by early neuropathologists based on postmortem material (Bouchet and Cazauvieilh 1825). Only later was the potential importance of this lesion in epilepsy recognized (Gloor 1997; Thom 2009). Autopsy and neuroimaging studies indicate that patients with MTLE with HS often have bilateral asymmetric hippocampal damage, with one side showing HS and the other side with varying degrees of hippocampal damage, ranging from mild non-specific neuronal loss to well-characterized milder HS (Gloor 1997; Meencke 2009).

Since first histological descriptions, the question of whether HS is a cause or consequence of seizures has been raised (Gloor 1997; Cendes 2005). This is a controversial issue, and as in many other biological issues, the answer is most likely to lie in between.

Different lesions involving hippocampus have been extensively studied in different types of animal models, each having features of cell loss and plasticity similar to those observed in surgical specimens of patients with MTLE with HS (Schwartzkroin 1993; Gloor 1997). By comparing these models, different conclusions may emerge regarding the role of discrete or intense cell loss, mossy fiber sprouting, and other histochemical features (Franck and Schwartzkroin 1985; Gloor 1997). In spite of these differences, it is clear that the

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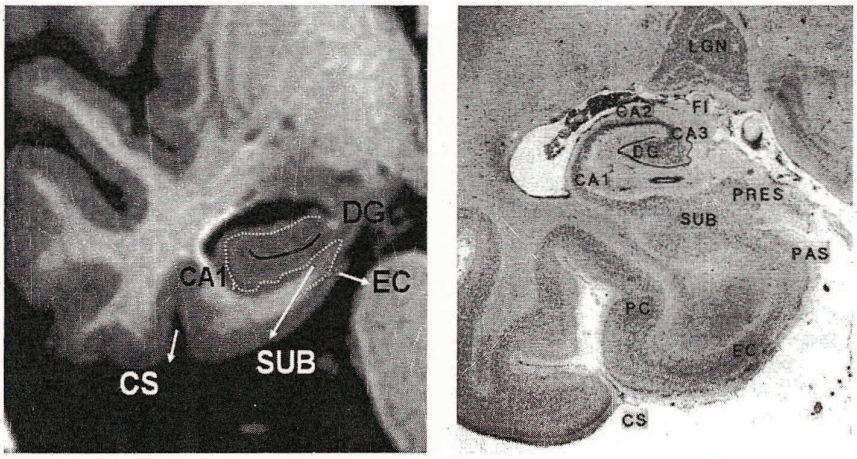

Fig. 53.1. The medial temporal region (MRI illustration and histological detail) at the level of the posterior tip of uncus illustrating the hippocampal subfields and related structures. CA1, CA2, and CA3 indicate sectors cornu Ammonis 1, 2, and 3; CS, collateral sulcus; DG, dentate gyrus; EC, entorhinal cortex; FI, fimbria; LGN, lateral geniculate nucleus; PRES, presubiculum; SUB, subiculum.

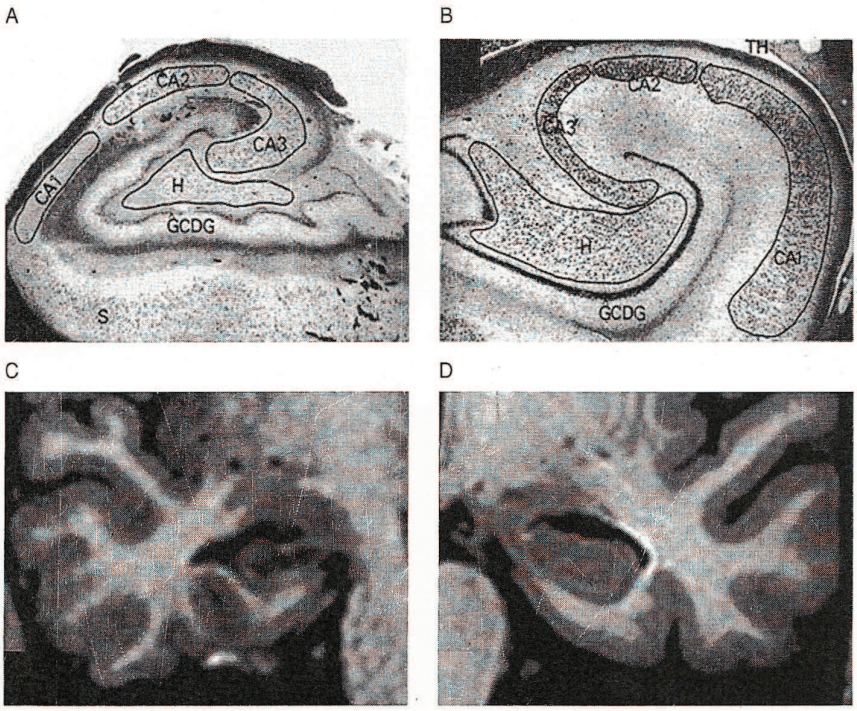

Fig. 53.2. Typical histology picture and MRI (T1-weighted image) from hippocampal sclerosis (A and C) and from a normal hippocampus (B and D). Note the relative sparing of subfield CA2 as opposed to the intense cell loss in CA1 and CA3 in (A) as compared to (B). (C) An atrophic hippocampus with loss of internal structure and hypointense T1 signal. (Panels A and B were modified from Van Paesschen *et al.* [1997].)

clinical manifestation of MTLE depends on a critical combination of these morphological changes. However, there is also evidence that even if complete HS is produced experimentally, seizures may not develop (Schwartzkroin 1993). These findings, in addition to several others (Cendes 2005), may indicate that HS and seizures are signs and symptoms of a complex underlying pathological process, and that they may evolve concomitantly. While HS may be produced by seizures (in particular during status epilepticus), the development of MTLE as a syndrome does not depend solely on cell loss or plasticity in the hippocampus. This would be a gross oversimplification that cannot account for common associated features, as for example, the high incidence of depression in MTLE (Kanner 2006).

Hippocampal sclerosis has all the hallmarks of an inert lesion acquired in the remote past and seems to be both a cause and a consequence of seizures: a cause as supported by evidence, discussed below, that HS may come before the development of seizures, and a consequence as supported by clinical and experimental evidence indicating progressive neuronal damage and synaptic reorganization secondary to seizures (Mathern *et al.* 2002; Cendes 2005).

The mechanisms underlying the development of HS remain undetermined. The condition most likely has different causes in different individuals, and may result from complex interactions among genetic and environmental factors.

Initial precipitating injury

In the early 1950s Penfield defended the hypothesis that HS was caused by transtentorial herniation of the mesial temporal lobe during birth. This herniation would cause an ischemic lesion termed incisural sclerosis that with time would cause

epilepsy (Earle *et al.* 1953). Meyer and Falconer (1954) stated that in addition to a history of difficult birth, there were other factors related to HS, including head trauma and, in particular, prolonged febrile seizures (FS) in early childhood; this became known as Meyer's hypothesis. However, population-based studies have not shown a significant relationship between FS early in life and subsequent MTLE (Cendes 2005). The interpretation of these observations remains controversial. One possibility is that the early FS damages the hippocampus and is therefore a cause of HS. Another possibility is that the child has a prolonged FS because the hippocampus has previously been damaged due to a prenatal or perinatal insult or to a genetic predisposition. The first interpretation would favor the hypothesis that more frequent seizures would cause more severe HS, and the second would be in favor of more severe HS causing more severe seizures. In either hypothesis, a cross-sectional, retrospective analysis would result in a positive correlation between seizure frequency and degree of HS, thus not solving the enigma of cause or consequence (Cendes 2005).

Recent studies have shown that prolonged and focal FS can produce acute hippocampal injury that evolves to hippocampal atrophy and that complex FS can actually originate in the temporal lobes in some children. Although there is a high incidence of complex FS among patients with mesial temporal sclerosis in retrospective studies, it is still not clear whether complex FS are an epiphenomenon or a causative factor (Mathern *et al.* 2002).

Chemoanatomical studies have shown that the vulnerable sectors of the hippocampus are rich in kainate (endfolium and sector CA3) and N-methyl-D-aspartate (NMDA) receptors (sector CA1) (Schwartzkroin 1993; Gloor 1997). Activation of NMDA receptors and of a subclass of kainate receptors leads to considerable Ca^{2+} influx into postsynaptic neurons and if, as is the case in prolonged seizures, these neurons are not protected by Ca^{2+}-binding proteins, they may become irreversibly damaged and die. In the human hippocampus, the principal cells of the vulnerable sector, i.e., the endfolium, sectors CA3 and CA1, contain virtually no Ca^{2+}-binding proteins (calbindin or parvalbumin), while the relatively resistant structures such as the dentate granule cells and sector CA2 are rich in calbindin (Gloor 1997). The destruction of neurons in the vulnerable sectors of the hippocampus that characterizes HS, may thus be the consequence of two of their chemoanatomical features: (1) the high content of the type of glutamate receptors that promotes Ca^{2+} entry into the neuron during a seizure, and (2) their lack of protection against Ca^{2+} overload due to their virtual lack of Ca^{2+}-binding proteins. A similar profile of hippocampal vulnerability to seizures presumably caused by the same pathogenetic mechanism is also seen in some experimental models of epilepsy (Schwartzkroin 1993; Gloor 1997).

This pathogenetic explanation fails, however, to account for the cause of the frequent unilaterality of HS. It is possible that both prolonged FS (which have commonly a unilateral predominance) and the ensuing damage have been primed by some pre-existing hippocampal damage.

Genetic predisposition appears to be an important causal factor in patients with HS and antecedent prolonged FS (Berkovic and Scheffer 1998; Kobayashi *et al.* 2001, 2002). Recent clinical and molecular genetic studies show that there is some specificity in the types of epilepsy that follow FS, rather than FS being a non-specific marker of a lowered seizure threshold. The relationship between FS and later development of epilepsy is frequently genetic and there are a number of syndrome-specific genes for FS (Berkovic and Scheffer 1998).

Recent evidence from experimental and clinical studies also provides data suggesting the importance of innate immunity in the etiology and pathogenesis of MTLE. The presence of inflammatory processes, indicated, for example, by the presence of highly upregulated chemokines genes in chronic MTLE (van Gassen *et al.* 2008) may directly and indirectly affect neuronal excitability. Early upregulation of chemokines, for instance after a viral infection, trauma, FS, tumors, or other infections, may be a common pathway linking initial precipitating injuries (IPIs) in the etiology of MTLE. There has been evidence of a possible role of complement activation and other inflammatory pathway involvement in both experimental and human MTLE (Aronica *et al.* 2007; van Gassen *et al.* 2008). Indeed recent studies indicate that the role of viral infection in the etiology of MTLE might be underestimated (Donati *et al.* 2003).

Falconer and Taylor (1968) developed the concept that HS is both a cause and also a consequence of epileptic seizures, which has been supported by more recent investigations (Cendes 2005; Meencke 2009). In fact, by expanding the concept of IPI to include any significant medical event likely to injure the brain before the onset of seizures, such as prolonged FS, trauma, hypoxia, and intracranial infection, studies of surgical series of MTLE have found a strong association between HS and IPI (Mathern *et al.* 2002). These studies support the concept that HS is likely an acquired pathology, and most of the neuronal loss occurs with the IPI; however, ongoing frequent seizures do cause additional progressive hippocampal damage (Mathern *et al.* 2002; Cendes 2005; Bonilha *et al.* 2006).

Familial mesial temporal lobe epilepsy

Studies in familial MTLE are also important for better understanding of the pathogenesis of HS.

Signs of HS were present in MRI scans of subjects with familial MTLE (Kobayashi *et al.* 2001; Andrade-Valenca *et al.* 2008) and in some asymptomatic family members (Kobayashi *et al.* 2001, 2002). These findings alone suggest that hippocampal abnormalities associated with HS are not the sole consequence of repeated seizures and that genetically determined mechanisms might play an important role in the development of hippocampal damage, which may be hereditary, at least in these familial cases (Kobayashi *et al.* 2001).

Most affected individuals with familial MTLE have a benign clinical course, and in some families all affected members have good seizure control or remit after a short period of seizures. However, as in patients with non-familial MTLE, some affected family members may have poor seizure

control and require surgical treatment. Although MRI signs of HS, including hippocampal atrophy and hyperintense T2-weighted signal, are more frequent and more pronounced in patients with refractory seizures, these changes are also observed in patients with a good clinical outcome, and even in asymptomatic family members. These are strong indicators that genetic factors play a role in the genesis of hippocampal pathology in patients with familial MTLE. While the pattern of inheritance is autosomal dominant with incomplete penetrance, the genetic background in familial MTLE does not imply a more widespread structural abnormality on MRI.

The presence of HS in both affected and asymptomatic family members in familial MTLE suggests that the hippocampus abnormalities themselves could be inherited, and not necessarily lead to epilepsy (Kobayashi *et al.* 2002). The phenotype would then be dependent on interaction with other modifying factors. These data together with the existence of a number of syndrome-specific genes for FS emphasize the importance of genetic factors as one of the causes of HS.

Available qualitative pathology from surgical specimens obtained from operated familial MTLE patients showed the typical pattern of HS: selective neuronal loss in CA1, CA3, and CA4 with relative preservation of CA2, and variable involvement of the amygdala and parahippocampal region (Kobayashi *et al.* 2003). The observation of HS in operated Familial MTLE patients who became seizure-free suggests that HS represents the epileptogenic substrate, at least in some of these families, analogous to what is observed in non-familial or "sporadic" cases. One study looked further into hippocampal cell densities and intensity of supragranular mossy fiber staining in postoperative tissues from patients with familial and sporadic MTLE (Andrade-Valenca *et al.* 2008). Patients with familial MTLE present most histological findings comparable to patients with sporadic MTLE; however, mossy fiber sprouting was less pronounced in patients with familial MTLE, suggesting that they respond differently to plastic changes plausibly induced by cell loss, neuronal deafferentation, or epileptic seizures when compared to sporadic MTLE (Andrade-Valenca *et al.* 2008).

Most likely, familial MTLE will be found to have a major gene leading to hippocampal abnormalities, and the phenotype could be influenced by additional genetic and environmental modifying factors, including known and unknown IPIs or unidentified environmental injuries.

Magnetic resonance imaging studies

It has been widely accepted, based on large series of surgical patients, that there is a strong correlation between HS and the severity of the epilepsy. Hippocampal sclerosis identified by MRI has been associated with poor medical control of seizures by Semah *et al.* (1998). However, the findings of MRI abnormalities in patients with good outcome or seizure remission, indicates that MTS is found not only in patients with medically refractory TLE (Kobayashi *et al.* 2001). Evidence for this has already been hinted at in the literature, including descriptions of sporadic patients with HS (Kim *et al.* 1999). Furthermore, there is upcoming MRI evidence of MTS acquired in adulthood (Briellmann *et al.* 2001) not necessarily associated with poor seizure control (Kobayashi *et al.* 2002; Cardoso *et al.* 2006).

Neuropathological studies

Recent molecular neuropathological studies focusing on developmental aspects of hippocampal organization revealed two intriguing findings in HS specimens of MTLE patients who underwent surgery: (1) the persistence of Cajal-Retzius cells in HS patients points towards an early insult and an altered Reelin signaling pathway and (2) increased neurogenesis in and abnormal architectural organization of the dentate granule cell layer can be observed in young patients with early hippocampal seizure onset (Blumcke *et al.* 2002, 2009). These findings suggest a developmental malformation of the hippocampus (inherited or acquired) that in association with other subsequent injury during life (e.g., trauma, infection, FS) could develop ongoing seizures, then resulting in the full-blown neuropathological features of HS (Blumcke *et al.* 2002).

There seems to be in association with neuronal loss, presence of aberrant axons, and synaptic reorganization in human HS. Studies have described synaptic reorganization of the mossy fibers system (the axons of the dentate granule neurons). Mossy fiber sprouting is characterized by the formation of novel, aberrant synaptic contacts of mossy fibers onto the proximal dendrites of the hippocampal dentate granule neurons. This aberrant circuitry is probably related to epileptogenesis by changes in excitatory and inhibitory processes (Blumcke *et al.* 2002; Sutula 2004).

Laboratory studies

Some laboratory studies have provided significant data for understanding the epileptogenesis in HS. Some studies suggest that the affected hippocampus has some important functional differences when compared to the "normal" hippocampus, for example structural changes such as sprouting, neurotransmitter and receptor changes, modification in ion channels, water channels, changes in mitochondrial and glial function, and also signs of inflammatory processes (Aronica *et al.* 2007; van Gassen *et al.* 2008; Blumcke *et al.* 2009; Meencke 2009; Thom 2009).

Pathophysiology: progression

Studies have shown progression of neuronal damage and dysfunction in patients with MTLE and HS (Cendes 2005). However, it is still unclear why, when, and how neuronal damage and dysfunction occur in these patients. Seizure frequency is considered the most important factor for progression of damage and dysfunction in MTLE with HS. Nevertheless, it is possible, for example, that not all types of seizures do cause harm, or yet that some individuals are more resistant to seizure-induced damage than others (Schwartzkroin 1993; Gloor 1997; Brandt *et al.* 2004; Cendes 2005). Genetic background, age, and

type of initial brain insult, and other environmental factors, most likely interact in a number of ways, making it difficult to determine what are the exact mechanisms of ongoing brain damage in MTLE (Cendes 2005).

Furthermore, mechanisms that are responsible for, or influence, the development of an epileptic condition differ from those that actually precipitate acute epileptic seizures. Another complication is the fact that seizure-related damage may be expressed in a number of ways, and does not necessarily represent neuronal loss or atrophy. For example, many patients with MTLE who do not respond well to treatment have progressive memory loss and signs of diffuse cognitive impairment, as well as progressive increase of bilateral epileptiform discharges (Morrell 1989; Gloor 1997). These observations suggest that focal epileptic discharges may lead to neuronal dysfunction remote from the seizure focus.

Epilepsy and hippocampal sclerosis

Risk factors

As discussed above, familial history seems to be one of the risk factors for HS, as well as prolonged FS and other brain injuries in early childhood, although these factors have been described mostly in surgical series (Cendes 2005) and have not been clearly confirmed in population-based studies (Camfield *et al.* 1994).

Type of epilepsy

Clinical presentation

The natural history of MTLE with HS is classically described as a latent period between IPI and/or onset of seizures, although the IPI is often not identifiable. Seizures may be initially well controlled for some time before they become medically refractory. However, not all patients with MTLE and HS become refractory and it is not uncommon to encounter patients without a typical history, particularly in the familial forms (Wieser 2004).

The first habitual seizures usually occur in late childhood or early adolescence. The initial ictal event may be a generalized convulsion or a complex partial seizure. Complex partial seizures are usually preceded by an aura, typically involving epigastric rising sensation associated with an emotional disturbance such as fear. Other psychic (e.g., déjà vu) and autonomic symptoms (e.g., flushing, pallor, tachycardia) are also seen, and some patients can have olfactory or gustatory sensations. Auras typically occur in isolation (simple partial seizures), as well as in association with complex partial seizures (Cendes *et al.* 2002a).

The complex partial seizure commonly begins with a motionless stare and oroalimentary automatisms (e.g., lip smacking, chewing) with a progressive clouding of consciousness. Gestural automatisms, as well as reactive automatisms that can be ictal or postictal, are also common. When posturing of one extremity occurs, it is contralateral to the side of ictal onset. Hand automatisms are frequent and tend to be ipsilateral to the HS, mainly when associated with a contralateral dystonic posturing. Verbal automatisms may be present in seizures originating in the non-dominant hemisphere. There is transient postictal disorientation and, with onset in the language-dominant hemisphere, there may also be some degree of postictal aphasia. Postictal nose-wiping may occur, usually with the hand ipsilateral to the seizure onset. Patients are frequently amnesic of the ictal phase, even though they may make semi-appropriate responses during the seizure. The aura, however, is usually remembered.

Seizures typically last 1 to 2 min and are relatively stereotyped in a given patient. Patients may recall occasional auras years before they experienced the first habitual complex partial seizure. Precipitating factors include stress, sleep deprivation, and, in women, hormonal changes associated with the menstrual cycle. Secondary generalization as well as status epilepticus are infrequent, but may occur (Cendes *et al.* 2002a).

There are no definitive characteristics that distinguish complex partial seizures in MTLE with HS from complex partial seizures generated in the anterior portion of the temporal lobe. The classic presentation as described above may be similar to ictal symptoms described by patients with mesio temporal lesions other than HS or without any detectable MRI abnormalities. For this reason, the accurate diagnosis of MTLE is based on a constellation of signs and symptoms and diagnostic tests (Wieser 2004).

Seizures that begin with primary visual, auditory, or focal somatosensory auras, focal, or violent motor behaviors and extratemporal electroencephalogram (EEG) spikes do not fill clinical criteria for MTLE with HS (Cendes *et al.* 2002a; Wieser 2004).

Diagnostic principles

The diagnosis of MTLE requires a constellation of signs and symptoms, but the most important is the presence of characteristic seizure semiology (Wieser 2004). The accurate recognition of MTLE with HS is usually based on MRI findings, EEG and video-EEG, neuropsychological tests, and sometimes positron emission tomography (PET) and single photon emission computed tomography (SPECT).

Neurologic examination is usually normal except for facial asymmetry and memory deficits, which are material-specific for the side of ictal onset (Jones-Gotman and Smith 2006).

Diagnostic tests

Genetic tests

There is no genetic test available yet for diagnosis of HS.

Histological tests

Histopathological hallmarks include segmental loss of pyramidal neurons, granule cell dispersion, reactive gliosis, and axonal sprouting of surviving neurons. The neuronal loss and gliosis involve hippocampal sectors CA1, CA3, hilus, and

dentate gyrus, in addition to granule cell dispersion, with relative sparing of CA2 and subiculum (Thom 2009). The neuronal damage often involves also the amygdala, uncus, and parahippocampal gyrus.

Neurophysiological test

Interictal electroencephalography

Interictal EEG findings in patients with MTLE typically include unilateral or bilaterally independent mesial temporal spikes, best seen with basal (sphenoidal, inferior temporal) derivations.

Temporal intermittent rhythmic delta activity appears to have a localizing value of the epileptogenic zone in MTLE, unlike intermittent rhythmic delta activity in other brain regions (Cendes *et al.* 2002a).

Ictal electroencephalography

Ictal EEG recordings usually reveal a characteristic ictal pattern consisting of regular well-lateralized rhythmic 5–9-Hz activity in one anterior-mid and infero-mesial temporal region, before the first clinical manifestations, or within 30 s (delayed focal onset), with or without contralateral propagation.

Ictal discharges may be confined to the medial temporal structures for a few seconds or even longer, without evident EEG changes on scalp recordings. This may be followed by a fast propagation of ictal discharges to the ipsilateral or contralateral temporal neocortex, or it may propagate to both hemispheres in a diffuse fashion. In these circumstances, the scalp EEG record may miss the initial (truly localizing) seizure discharges. Thus, ictal scalp EEG recordings may have limited localizing value when the first clinical manifestations clearly precede the first EEG changes. This false localization phenomenon may be associated with severe hippocampal damage (Mintzer *et al.* 2004).

Intracranial recordings

Although diagnosis of MTLE with HS and identification of the side of ictal onset for surgical therapy is now possible in the majority of patients using non-invasive investigation (Diehl and Luders 2000), when the side of mesial temporal ictal onset is unclear, or there remains a possibility of neocortical ictal onset, additional long-term monitoring with intracranial electrodes is appropriate. Most centers utilize depth electrodes for this purpose, but subdural strips or grids and foramen ovale electrodes can also be used (Cendes *et al.* 2002a).

Biochemical tests

There are no biochemical markers for HS.

Immunological tests

There are no immunological tests available. However, there are recent investigations towards immunological aspects in MTLE as discussed above (Aronica *et al.* 2007; van Gassen *et al.* 2008).

Table 53.1 Imaging of hippocampal sclerosis

Magnetic resonance imaging (MRI)
Detects most MTS
Abnormalities highly specific to MTS
Insensitive to epileptogenicity
Magnetic resonance spectroscopy (MRS)
Detects metabolic changes in mild to severe MTS
Interictal [^{18}]F-fluorodeoxyglucose positron emission tomography (FDG PET)
Detects metabolic changes in mild to severe MTS
Highly sensitive to epileptogenicity, not specific to MTS
Ictal single photon emission computed tomography (SPECT)
Highly sensitive to epileptogenicity, not specific to MTS

Neuroimaging

A summary of neuroimaging findings of HS is presented in Table 53.1.

Magnetic resonance imaging

High-resolution MRI is a highly sensitive and specific non-invasive method to diagnose HS in vivo. Images need to be optimized for the evaluation of features indicating hippocampal pathology. Coronal slices are mandatory and they need to be obtained on a plane perpendicular to the long axis of the hippocampus guided by a sagittal scout image. The slices need to be thin to allow appreciation of fine details of the different portions of hippocampal anatomy. Ideally, the slice thickness should be 3 mm or less, and never more than 5 mm. To evaluate volume, shape, orientation, and internal structure, high resolution T1-weighted images, particularly with inversion recovery (IR), are essential. T2-weighted or fluid attenuation inversion recovery (FLAIR) images are important to assess qualitatively the signal intensity.

Visual discrimination of a normal from an abnormal hippocampus is straightforward when one is clearly normal and the other is grossly abnormal, but the visual binary paradigm breaks down in the presence of symmetric bilateral disease or mild unilateral disease. In this case volumetric MRI can be used to detect mild unilateral disease or bilateral hippocampal volume loss. Most radiologists can detect visually a side-to-side asymmetry ratio of 80% or less.

A majority of patients with HS undergoing presurgical evaluation will have a clear-cut unilateral atrophic hippocampus with increased T2-weighted signal and a normal appearing contralateral hippocampus (Fig. 53.3). Therefore, qualitative visual analysis is quite sensitive, especially if the MR images are carefully and properly acquired (Kuzniecky *et al.* 1997).

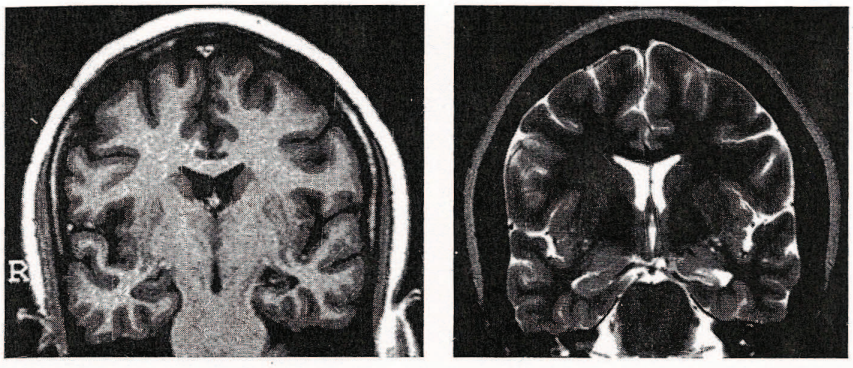

Fig. 53.3. T1-weighted inversion recovery and T2-weighted coronal MRI from a patient with left HS who underwent selective amygdalohippocampectomy and became seizure-free. Observe the atrophy, loss of internal structure, hypointense signal on T1-weighted, and hyperintense signal on T2-weighted image.

In surgically treated MTLE–HS the usual hippocampal abnormalities are:

- Atrophy (detected with MRI in 90–95% of cases in which HS is found in resected tissue)
- Loss of internal architecture (in 60–95%)
- T2-weighted increase (in 80–85%)
- T1-weighted decrease (in 10–95%).

The commonly occurring extrahippocampal abnormalities are:

- Atrophy-signal alterations of the ipsilateral amygdala, temporal neocortex, temporal lobe white matter, fornix, mamillary body, insula, thalamus, or basal frontal cortex
- Atrophy-signal alterations of the contralateral hippocampus (less severe than ipsilateral hippocampal alterations)
- Dilatation of the ipsilateral or contralateral temporal horn of the lateral ventricle (often a "falsely lateralizing" finding, in that temporal horn dilatation often is more severe on the side contralateral to the sclerotic hippocampus). Diffuse hemispheric atrophy can occur ipsilaterally in MTLE–HS, but is rare.

More detailed high-resolution MRI analyses reveals a network of gray matter atrophy that involves mesial temporal and other structures interconnected with the limbic system, including amygdala, entorhinal, perirhinal and parahippocampal cortices, and thalamus.

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (MRS) studies have shown focal reductions of *N*-acetylaspartate (NAA) signal in MTLE with HS, including patients with normal MRI. Both single-voxel and multivoxel [^{1}H]MRS have high sensitivity for detecting low NAA indicative of neuronal dysfunction in focal epilepsies. Decreases in NAA correlate strongly with EEG abnormalities and severity of cell loss, and may be a more sensitive measure than structural MRI. However, the NAA decrease is often more widespread than the epileptogenic focus (Cendes *et al.* 2002b).

Proton MRS studies have shown recovery of relative NAA either ipsilaterally or contralaterally after successful temporal lobe removal. This suggests that structural or functional changes associated with seizure activity may lead to depression of NAA in the ipsilateral and contralateral temporal lobe (Cendes *et al.* 2002b).

Positron emission tomography and single photon emission computed tomography

The same temporal lobe with HS is usually hypometabolic on interictal [^{18}F]flurorodeoxyglucose (FDG) PET with an area that involves the mesial structures, the pole, and part of the lateral cortex, which is helpful and reliable in localizing temporal lobe foci for surgical treatment (Wieser 2004).

The area of decreased flumazenil binding, as assessed by [^{11}C]flumazenil-PET, is often smaller than that of glucose hypometabolism, since it is thought to largely reflect an underlying neuronal loss (Koepp *et al.* 1997).

Logistical and other difficulties (such as high cost and the need for a local cyclotron for PET) limit accessibility to these techniques and they are not routinely used in most institutions.

Ictal and early postictal SPECT scans are also helpful in localizing the epileptogenic focus in patients with TLE (Velasco *et al.* 2002).

Interictal SPECT may reveal an area of temporal hypoperfusion, but it is not reliable and should be performed only for the purpose of comparison with ictal SPECT, particularly by using ictal–interictal subtraction images co-registered to MRI (O'Brien *et al.* 1998). True ictal injections almost always show hyperperfusion of the whole temporal lobe with hypoperfusion of the surrounding cortex.

Neuropsychological tests

Neuropsychological evaluation commonly demonstrates memory dysfunction, which is material-specific according to the hemisphere involved and has been correlated to the degree

of HS as measured by postoperative histopathology and by hippocampal volumetry. Verbal memory is mostly affected with left-sided HS, whereas visuospatial memory is more affected with right HS (Jones-Gotman and Smith 2006).

Principles of management

Therapeutic principles

Treatment is based on the patient's response to antiepileptic drugs (AEDs) since some patients, especially those with familial MTLE, may have good seizure control with low doses of any of the AEDs indicated for partial epilepsies.

Treatment should start with a first-line AED in monotherapy, the dose of which is increased until seizure freedom or the occurrence of side effects such as tiredness, dizziness, diplopia, or gait disturbance. No data are available showing superiority of one AED over another, so that those drugs with fewer side effects should be preferred (Glauser *et al.* 2006).

The choice of first AED will determine the subsequent strategy and should be made with an element of forethought. The list includes phenytoin, carbamazepine, sodium valproate, lamotrigine, oxcarbazepine, topiramate, or levetiracetam (Kwan and Brodie 2004).

Seizures usually respond well for several years. Once seizures return very high levels of AED may be effective, but usually high-dose monotherapy results in intolerable side effects and fails to control disabling seizures (Cendes *et al.* 2002a; Kwan and Brodie 2004).

When monotherapy fails, combinations can be useful, but interactions and side effects should be considered and monitored carefully.

Carbamazepine and/or phenytoin as monotherapy are appropriate medications for management of MTLE. Higher serum levels than those used for generalized convulsions may be necessary, and medication should be increased until seizures stop or unacceptable side effects occur. Oxcarbazepine has an efficacy similar to that of carbamazepine, but some patients may tolerate higher dosages with fewer side effects, and in some cases this can make a difference in seizure control. Valproate, topiramate, lamotrigine, levetiracetam, or other broad-spectrum AEDs are sometimes of benefit when carbamazepine and phenytoin fail. A combination of drugs may be helpful for some patients, in particular clobazam associated with carbamazepine or phenytoin. When seizures become refractory to medical treatment, they are unlikely to remit spontaneously. With a long duration of uncontrolled seizures, increasing memory problems and other behavioral disturbances are usually reported. This sequence of events is a further suggestion that MTLE with HS may be a progressive epileptic disorder.

Surgical management

Definitions for medical intractability may vary among centers, but it usually includes failure to achieve seizure control with two or more AEDs with adequate dosage and posology. The decision as to when one should perform surgery may be more difficult and controversial. Delaying surgery, however, while running through a range of AED monotherapies and combination options may worsen the long-term prognosis (Yoon *et al.* 2003).

Because of the psychosocial consequences of disabling epilepsy in adolescence and early adulthood, patients who may have MTLE with HS should be referred to epilepsy centers as soon as it is apparent that control cannot be achieved with first-line medication. Surgery is worth considering because the long-term postoperative prognosis is very good (McIntosh *et al.* 2004). Patients with MTLE and unilateral HS are excellent candidates for surgical treatment, with a 60–80% chance of becoming free of disabling seizures (Wiebe *et al.* 2001). However, the frequency of complete seizure freedom drops to 47% in 5 years and 41% in 10 years of follow-up (McIntosh *et al.* 2004).

The presurgical evaluation should be made considering clinical factors, EEG, preoperative MRI, neuropsychological evaluation, and often functional imaging with either PET or SPECT as discussed above (Wieser 2004).

The choice of whether to perform an anterior temporal lobectomy or to take a more selective approach depends on the surgical teams. Whether this influences the postoperative neuropsychological outcome is still uncertain.

While outcome following a temporal lobectomy is most often thought of in terms of postoperative seizure control, the most common serious cognitive complication of surgery is a postoperative decline in verbal memory following a dominant temporal lobectomy. The clear link between functional and anatomic integrity has lead to the evaluation of hippocampal volumetric measurements as a means of predicting postoperative memory decline. Patients at greatest risk for a decline in verbal memory following a dominant left temporal lobectomy are those with bilaterally symmetric severe hippocampal atrophy. Patients at next greatest risk are those with a volumetrically normal hippocampus (i.e., no atrophy). Patients with less risk for a postoperative verbal memory are those with significant unilateral left hippocampal atrophy.

There are a number of other postoperative issues that occur infrequently, which include visual field problems, double vision, word-finding problems, and other, usually subtle, neuropsychological concerns. In several cases, these problems are transitory. In addition, postoperative psychiatric disturbances may occur, including de novo psychiatric symptoms. Depression, anxiety, and psychosis are the most frequently reported postsurgical psychiatric disturbances (Foong and Flugel 2007). Whilst there are no absolute psychiatric contraindications to surgery, certain pre-existing psychiatric conditions may need careful consideration as there may be a risk of postsurgical psychiatric complications. A history of postictal psychosis, which is often associated with bilateral independent ictal foci and diffuse brain damage, has been associated with poor postsurgical seizure outcome (Alper *et al.* 2008).

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Dear Fernando Cendes

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