ELIANE KOBAYASHI

Este exemplar corresponde à versão final da Tese de Doutorado apresentada ao Curso de Pós-Graduação em Ciências Médicas da Faculdade de Ciências Médicas da UNICAMP, para obtenção do título de Doutor em Ciências Médicas, Área Neurologia da aluna **Eliane Kobayashi.**
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Prof. Dr. Fernando Cendes
Orientador

EPILEPSIA DE LOBO TEMPORAL FAMILIAR:

aspectos clínicos e investigação por ressonância magnética

CAMPINAS

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Tese de Doutorado apresentada à Pós-Graduação em Ciências Médicas da Faculdade de Ciências Médicas da Universidade Estadual de Campinas, para obtenção do título de Doutor em Ciências Médicas, área de Neurologia.

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Aluna: Eliane Kobayashi

Orientador: Prof. Dr. Fernando Cendes

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Projeto de doutorado desenvolvido nos Departamentos de Neurologia e Genética Médica da Faculdade de Ciências Médicas da Universidade Estadual de Campinas (UNICAMP), com suporte científico e financeiro da **Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) – processo 99/10702-3**, com início em fevereiro de 2000.

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DEDICATÓRIA

Aos meus queridos pais, Roberto e Ligia,

pelo exemplo de dignidade,

por todo o amor e compreensão.

À **FAPESP**, pelo apoio científico a este projeto.

Ao **Prof. Dr. Fernando Cendes** e à **Profa. Dra. Íscia Lopes-Cendes**, pela confiança depositada em mim para a condução deste projeto.

> *Não há modo de ensinar mais forte e suave do que o exemplo: persuade sem retórica, reduz sem porfia, convence sem debate, todas as dúvidas desata e corta caladamente todas as desculpas* (Padre Manuel Bernardes).

Às amigas **Andréa Alessio** e **Cristina Ferrari**, pela inestimável ajuda na avaliação dos meus pacientes.

À **minha família**, pelo apoio em tantos momentos difíceis.

A sabedoria da vida

não consiste em fazer aquilo que se gosta,

mas gostar daquilo que se faz

Leonardo da Vinci

PÁG.

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AH	atrofia hipocampal
CA1, CA2, CA3, CA4	subdivisões citoarquitetônicas do *cornu ammonis* (1, 2, 3, 4)
CF	crise epiléptica febril
CPS	crise parcial simples
CPC	crise parcial complexa
CTCG	crise tônico-clônica generalizada
DAE	droga anti-epiléptica
EH	esclerose hipocampal
ELT	epilepsia de lobo temporal
ELTM	epilepsia de lobo temporal mesial
ELTMfamiliar	ELTM familiar
ELTL	epilepsia de lobo temporal lateral
ELTLfamiliar	ELTL familiar
EMT	esclerose mesial temporal
EEG	eletroencefalograma
ILAE	International League Against Epilepsy
RM	ressonância magnética

RESUMO

As epilepsias familiares têm sido estudadas de forma abrangente nas últimas décadas e recentemente as formas familiares de epilepsia de lobo temporal (ELT) foram incluídas na nova classificação de síndromes epilépticas. Podemos dividir as ELT familiares conforme a semiologia das crises em mesial (ELTMfamiliar) e lateral/neocortical (ELTLfamiliar).

Na ELTMfamiliar os pacientes podem apresentar diferentes graus de severidade da epilepsia, desde remissão espontânea até crises refratárias. Atrofia hipocampal (AH) à ressonância magnética (RM) é freqüente e até o momento não foi esclarecida a base molecular envolvida na ELTMfamiliar.

A ELTLfamiliar é caracteristicamente benigna, apresenta ligação ao cromossomo 10q, crises com fenômenos auditivos e a RM é normal nas séries descritas.

Nosso objetivo foi determinar o padrão clínico da ELT familiar, correlacionando-o com achados de RM (incluindo indivíduos não afetados).

No ambulatório de epilepsia do Hospital das Clínicas da UNICAMP, identificamos 40 famílias com pelo menos dois indivíduos afetados (parentes em primeiro ou segundo grau) com critérios clínico-eletroencefalográficos para ELT. A análise dos heredogramas mostrou padrão de herança autossômica dominante com penetrância incompleta.

Nas famílias com ELTMfamiliar o número de afetados variou de 2 a 23 (média de 4,8). Estudamos um total de 194 indivíduos (sendo 52 não afetados), e apesar da maioria dos afetados apresentar boa evolução, 15% eram refratários ao tratamento clínico. Antecedente de crise epiléptica febril na infância foi identificada em apenas 11,5% dos pacientes.

AH associada à alteração de sinal foi identificada em 70% dos afetados e 34% dos assintomáticos, sendo mais severa e freqüente nos pacientes com crises refratárias. Alterações nos lobos temporais foram restritas às porções mesiais e atrofia da porção anterior do lobo temporal foi determinada em apenas 13,7% dos pacientes.

Vinte pacientes com ELTMfamiliar e crises refratárias foram submetidos a tratamento cirúrgico. Desses, 85% estão livres de crises após um a nove anos de seguimento. Fatores associados ao controle inadequado de crises no pós-operatório foram: volumetria normal,

AH e alterações eletroencefalográficas bilaterais. Sinais clássicos de esclerose mesial temporal (EMT), em graus variáveis, foram observados em 11/14 (79%) pacientes que tiveram estudo histopatológico qualitativo. Avaliação neuropsicológica (realizada em 30 indivíduos) mostrou associação de déficit de memória com crises refratárias e AH, com padrão semelhante ao descrito em pacientes não-familiares.

Apenas uma grande família com ELTL e ligação ao cromossomo 10q foi estudada. Todos os 18 pacientes avaliados apresentam ótimo controle de crises ou remissão. RM foi realizada em 22 indivíduos, incluindo assintomáticos. Malformação da porção lateral dos lobos temporais foi detectada em 10 (45%) pacientes.

As ELT familiares podem ser distinguidas quanto à semiologia das crises, tendo também perfil evolutivo e RM próprios. A ELTMfamiliar é mais prevalente, e o quadro clínico-histopatológico é indistinto de pacientes com ELTM não-familiar. AH é freqüente e nem sempre associada a crises refratárias, mas quando isto ocorre, o paciente apresenta excelente prognóstico cirúrgico.

Em conclusão, fica demonstrada 1) uma predisposição genética para AH em pacientes com ELTMfamiliar, sendo que 2) a variabilidade na severidade das crises deve ser influenciada por fatores modificadores, genéticos ou ambientais.

Apenas após a identificação do(s) gene(s) responsável(is) poderemos avaliar o exato papel desses fatores na determinação da apresentação clínica destes indivíduos.

ABSTRACT

Two forms of familial temporal lobe epilepsy (FTLE) are recognized according to seizure semiology: mesial (Familial MTLE) and lateral/neocortical (Familial LTLE).

Although originally described as benign and non-lesional, Familial MTLE has later been well characterized by the presence of both refractory patients and hippocampal atrophy (HA) on magnetic resonance images (MRI). To date, no genes have been identified. Familial LTLE is a benign epilepsy syndrome linked to chromosome 10q, with auditory auras, and no MRI abnormalities.

The objectives of this study were: 1) to determine clinical pattern in FTLE; 2) to study MRI characteristics in affected and unaffected family members; 3) to correlate MRI abnormalities with clinical presentation.

Families were identified in our epilepsy clinic (University hospital, UNICAMP), and had two or more affected individuals (first- or second-degree relatives) with clinical-EEG criteria for TLE. To date, we identified 46 families with FTLE (40 with Familial MTLE), and pedigree analysis showed autosomal dominant inheritance pattern, with incomplete penetrance.

The mean number of affected individuals in each family with MTLE was 4.8 (up to 23). Although most of affected individuals had a benign epilepsy course, 15% of them were medically refractory and needed surgical treatment. History of febrile seizures earlier in childhood was identified in only 11.5% of TLE patients.

MRI was performed in 194 individuals (142 affected and 52 unaffected). HA determined by volumetry, associated with hyperintense T2 signal, was identified in 70% of affected individuals and 34% of unaffected family members. HA was more frequent and more severe in patients with refractory seizures. Abnormalities in the temporal lobes were restricted to the mesial regions, and anterior temporal lobe atrophy was found in only 13.7% of patients.

Twenty patients with Familial MTLE and refractory seizures have been operated so far, and 85% of them are seizure-free (follow up varying from 1 to 9 years). From 17 available qualitative pathological reports, classical signs of mesial temporal sclerosis (MTS) were

seen in nine patients, with different degrees of gliosis and neuronal loss in CA1, CA3 and dentate gyrus.

Neuropsychological evaluation (performed in 30 individuals) showed an association of memory deficits with refractory seizures and HA, similar to non-familial MTLE patients.

Only one large family with LTLE and auditory auras linked to chromosome 10q was studied. All 18 evaluated patients have good seizure control or are seizure-free. MRI was performed in 22 individuals, including asymptomatics. Lateral temporal lobe malformations were found in 10 patients.

FTLEs can be distinguished according to seizure semiology, besides their characteristic clinical and MRI profiles. Familial MTLE is more prevalent and clinical-histopathological characteristics are similar to those found in non-familial patients. HA is quite frequent, and not necessarily associated with the presence of seizures or poor seizure control. In addition, refractory FMTLE patients have good post-operative results, despite the context of a familial epilepsy syndrome. The determination of the role of other environmental factors may be explored after the identification of the molecular basis in FMTLE.

CAPÍTULO 1

Introdução e Revisão da Literatura

EPILEPSIA DE LOBO TEMPORAL

Epilepsia de lobo temporal (ELT) é a forma mais comum de epilepsia parcial, acometendo pelo menos 40% de todos os pacientes adultos jovens com epilepsia. Na proposta para nova classificação de síndromes epilépticas da International League Against Epilepsy (ILAE), as ELTs foram denominadas *epilepsias límbicas* [Engel, 2001]. No entanto, optamos por manter o termo ELT, uma vez que esta nova classificação ainda não é definitiva.

Crises que se originam na porção mesial do lobo temporal, incluindo a amígdala, hipocampo e giro parahipocampal, constituem um subtipo distinto baseado na semiologia ictal, nos achados do eletroencefalograma (EEG), na patologia e na resposta à cirurgia. Há muito menos informação sobre a ELT neocortical, e a ocorrência de ilusões ou alucinações auditivas, ou um bloqueio súbito e precoce da fala no início da crise, indicam um envolvimento do córtex temporal lateral.

ELT MESIAL (ELTM)

A ELTM apresenta correlação freqüente com o achado histopatológico de EMT [Babb e Brown, 1987; Gloor, 1991; Meencke e Veith, 1991]. A importância clínica da ELTM dá-se pela sua alta prevalência e elevada proporção de pacientes que não respondem às diferentes drogas anti-epilépticas (DAEs), e que têm um bom prognóstico com o tratamento cirúrgico (80 a 90% de probabilidade de controle de crises) [Engel e Shewnon, 1993a; Engel et al., 1993b; Engel et al., 1997; Jack et al., 1992].

Manifestações clínicas

A ELTM apresenta um perfil clínico característico [Gloor, 1991]. A primeira crise "habitual" (que apresenta variações entre pacientes, mas é estereotipada ao longo da vida de cada paciente) ocorre geralmente no final da infância ou início da adolescência. O primeiro evento ictal pode ser uma crise tônico-clônica generalizada (CTCG) ou uma crise parcial complexa (CPC). No paciente em tratamento medicamentoso as CTCG secundárias são esporádicas, principalmente associadas a fatores precipitantes como *stress*, privação de sono e alterações hormonais. Entretanto, muitos pacientes nunca apresentam crises

generalizadas. Após um intervalo de tempo variável de bom controle ou remissão de crises, o paciente inicia com as suas crises habituais, geralmente do tipo CPC. História de crise epiléptica febril (CF) na infância é freqüente.

O exame neurológico é normal com exceção dos distúrbios de memória verbal ou não verbal de acordo com o lado acometido [Jones-Gotman, 1991; Jones-Gotman et al., 1993; 1997], e uma discreta paresia facial central, contralateral ao hipocampo atrófico [Cascino et al., 1993]. Os distúrbios de memória apresentam piora progressiva com crises freqüentes e podem melhorar com o controle das crises.

Prognóstico e complicações

A história natural da ELTM é pouco conhecida, pois apenas pacientes com crises refratárias às DAEs submetidos a tratamento cirúrgico, têm um diagnóstico anatomopatológico estabelecido. Em pacientes com crises não controladas com medicação é pouco provável que ocorra uma remissão espontânea [Engel et al., 1991; Engel et al., 1997; Sander, 1993; Sillanpaa et al., 1998] e aqueles com EMT unilateral ou bastante assimétrica são excelentes candidatos ao tratamento cirúrgico [Arruda et al., 1996]. Estudos retrospectivos sugerem que a ELTM é uma síndrome epiléptica causada por um insulto precoce [Cendes e Andermann, 2002; VanLandingham et al., 1998; Van Paesschen et al., 1997b], podendo a partir daí apresentar um caráter progressivo [Tasch et al., 1999; Mathern et al., 1996]. Entretanto, estudos prospectivos apresentam resultados controversos [Camfield et al., 1994; Shinnar, 1998; Shinnar, 2002].

Etiologia

Com o advento de novas técnicas de neuroimagem, incluindo análise estrutural e funcional, bem como avaliação qualitativa e quantitativa das estruturas do lobo temporal, tornou-se possível o diagnóstico "in vivo" das alterações associadas à ELTM.

Apesar da existência de casos de ELTM com ressonância magnética (RM) normal, a maior parte dos pacientes apresenta sinais indicativos de EMT. A EMT é caracterizada por esclerose hipocampal (EH) associada a um grau variável de gliose e perda neuronal na amígdala, uncus e giro parahipocampal [Bruton, 1988; Gloor, 1991; Meencke,

1991]. A EH consiste na perda neuronal com um padrão característico, envolvendo os setores CA1, CA3, hilus e giro denteado, com relativa preservação de CA2 [Babb e Brown, 1987; Gloor, 1991; Meencke, 1991].

A EMT foi primeiramente identificada por Bouchet e Cazauvieilh [1825] em exame "post-mortem" de pacientes com epilepsia mas acreditou-se que esta era uma conseqüência das crises epilépticas recorrentes. Evidência a favor do papel da EH como causa das crises, e da existência de uma síndrome clínica distinta, vieram do trabalho de Murray Falconer, um dos maiores defensores da ressecção temporal anterior "en bloc" para o tratamento das crises refratárias da ELTM [Falconer, 1953]. Estudos detalhados dos espécimes cirúrgicos demonstraram que a EMT é o substrato mais comum desta síndrome [Falconer, 1971].

A causa da EMT é desconhecida. Existe uma alta incidência de CFs complexas (crises febris prolongadas ou com sinais focais) em pacientes com EMT candidatos ao tratamento cirúrgico [Abou-Khalil et al., 1993; Cendes et al., 1993a; Cendes et al., 1993b; Hamati-Haddad e Abou-Khalil, 1998; Meencke e Veith, 1991; Shinnar, 1998]. Porém, há evidências sugestivas de que a EMT é a causa e não a conseqüência das crises recorrentes [Cendes et al., 1993c; Meencke e Veith, 1991].

Uma das maiores controvérsias em epileptologia é se crises recorrentes realmente causam dano adicional progressivo no cérebro. Alguns estudos [Cendes et al., 1993c; Kuks et al., 1993; Trenerry et al., 1993; Davies et al., 1996] sugerem que insultos cerebrais no início da vida são a principal causa de EMT, e que crises parciais recorrentes não produzem atrofia mesial adicional que possa ser quantificada macroscopicamente através da RM, porém outros estudos sugerem o contrário [Garcia et al., 1997; Kalviainen et al., 1998; Mouritzen Dam, 1982]. No entanto, CTCGs freqüentes ou CPC subentrantes, caracterizando estado de mal epiléptico, causam lesão adicional e aumento da atrofia hipocampal (AH) [Tasch et al., 1999; Theodore et al., 1999a; Theodore et al., 1999b]. Outras técnicas de neuroimagem, como a espectroscopia por RM, permitem a monitorização "in vivo" da integridade neuronal e, portanto podem detectar lesão ou disfunção progressiva, que não necessariamente reflete-se em atrofia [Tasch et al., 1999; Bernasconi et al., 2002].

A grande incidência de história familiar de epilepsia entre os pacientes com ELTM sugere uma predisposição genética [Falconer, 1971; Andermann, 1982]. Além disso, a descrição de casos familiares de ELT (discutido adiante), com alto índice de alterações hipocampais, indica a presença de fator(es) genético(s) como causa da EMT nos casos familiares de ELTM [Cendes et al., 1998; Kobayashi et al, 2001].

Critérios diagnósticos e investigação complementar

O diagnóstico das crises e da ELT depende, sobretudo, das características clínicas e do EEG [Comission on classification and terminology of the ILAE, 1981; 1989] e exames complementares podem confirmar o diagnóstico clínico. Nos pacientes com crises refratárias, estes exames são fundamentais para a lateralização e localização do início das crises, visando uma proposta cirúrgica.

Assim, os EEGs de rotina mostram atividade epileptiforme unilateral ou bilateral nas regiões temporais médio-basais, melhor observadas com a utilização de eletrodos zigomáticos e esfenoidais. Entretanto, alguns pacientes apresentam EEGs de rotina repetidamente normais, e isto não exclui o diagnóstico de ELTM. Os registros ictais revelam um início característico, (atividade rítmica de 5 a 7Hz) máxima em um dos eletrodos zigomáticos ou esfenoidais, seja como a primeira manifestação eletrográfica ictal ou dentro de 30 segundos após o início da crise, porém , outros padrões eletrográficos ictais podem ocorrer [Engel et al., 1993b; Spanedda et. al, 1997].

Na maioria dos pacientes com crises refratárias a RM mostra sinais indicativos de EMT: diminuição de volume do hipocampo, com alteração do formato e estrutura interna, além de aumento de sinal nas aquisições em T2. Podemos observar ainda atrofia de amígdala e do lobo temporal como um todo. A atrofia pode ser unilateral ou bilateral, em geral assimétrica. Em casos duvidosos, e para quantificação das alterações, pode-se empregar técnicas de volumetria, que possibilitam a detecção de atrofia com maior sensibilidade, e esta redução de volume correlaciona-se com as características histopatológicas de EMT [Cascino et al., 1991; Cendes et al., 1993a; Cendes et al., 1993b; Cendes et al., 1996; Jack et al., 1992; Lencz et al., 1992].

Além do estudo volumétrico, a identificação de sinal T2 intenso nas estruturas mediais do lobo temporal, presente em alguns pacientes com EMT, é um achado importante para o diagnóstico por imagem de patologia hipocampal. A quantificação do sinal T2 [Jackson et al., 1993; Kuzniecky e Jackson, 1995; Van Paesschen et al., 1997a; Van Paesschen et al., 1997b] associada ao estudo volumétrico pode fornecer informações adicionais sobre alterações destas estruturas.

A avaliação neuropsicológica pode detectar distúrbios de memória verbal e não verbal, conforme acometimento do hemisfério dominante e não dominante para linguagem, respectivamente. Esta disfunção tende a ser progressiva [Jones-Gotman, 1991] pode correlacionar-se com o controle inadequado de crises e é proporcional ao grau de atrofia das estruturas mesiais, sobretudo do hipocampo [Jones-Gotman et al., 1993; Jones-Gotman et al., 1997].

Questões sobre a ELTM

Recentemente, em encontro de especialistas em epileptologia e neuroimagem [Engel et al., 2002], foram discutidas questões referentes à ELTM, e vários aspectos desta síndrome foram revisitados:

Apresentação clínica: Não há uma idade específica de início das crises, apesar da primeira crise ocorrer geralmente entre 4 e 16 anos. Entretanto, a primeira crise habitual do paciente com EH tende a ser mais precoce que em pacientes com ELTM relacionada a outra etiologia.

Quanto à evolução das crises, alguns pacientes não apresentam um período latente. O período silente entre a primeira crise habitual e o início de crises refratárias é relatado, porém difícil de ser objetivado. CTCGs secundárias são raras devido à eficácia das DAEs, e provavelmente devido à propagação lenta a partir das estruturas mesiais temporais.

Há provavelmente formas benignas e refratárias de ELTM, mas apenas as formas refratárias foram bem caracterizadas (em centros terciários). Estudos prospectivos são necessários para caracterização da ELTM benigna e para sua determinação como uma

forma distinta dentro do *continuum* da ELTM. A resistência às DAEs não parece ser característica da ELTM associada à EH. No estudo de Stephen et al [2001], 42% dos pacientes com ELT e AH ficaram livres de crises. Já outras séries [Semah et al., 1998 e Kim et al., 1999], demostraram que apenas 11% e 25% dos pacientes com AH apresentavam boa evolução.

Características da ELTM associada à EH: Podemos dizer que há diferentes tipos de ELTM associada à EH: EH primária levando à ELTM, ELTM familiar associada à EH e EH secundária (por exemplo, após meningoencefalite herpética).

Há uma clara predisposição genética, uma vez que história familiar é freqüente entre pacientes com ELTM. Entretanto, nem todos podem ser agrupados numa mesma síndrome epiléptica familiar, podendo fazer parte de famílias com ELTM familiar, Epilepsia parcial com foco variável e Epilepsia generalizada com crises febris "plus".

Ainda não se determinou a existência de uma patofisiologia específica na ELTM. Não é possível afirmar quais das seguintes alterações são epileptogênicas e quais são efeitos inespecíficos da epilepsia: padrão de perda neuronal, gliose reacional, reorganização sináptica, epileptogenicidade e crises espontâneas. Além disso, não foi estabelecido se história de insulto precipitante inicial e predisposição genética são necessários para o processo patofisiológico.

No encontro de especialistas promovido pela ILAE, em maio de 2002 [Engel et al., 2002], com o objetivo de definir critérios diagnósticos para a ELTM associada a EH e definir se esta condição caracteriza uma doença específica, uma síndrome distinta ou um grupo de síndromes. O consenso deste painel de especialistas foi que nenhum critério clínico ou laboratorial isoladamente é suficiente para o diagnóstico de ELTM. No entanto, na nossa opinião, os três primeiros itens enumerados a seguir são os mais importantes para o diagnóstico de ELTM, e quanto maior o número de critérios combinados, maior a certeza diagnóstica.

Critérios diagnósticos para a ELTM associada a EH [Engel et al., 2002]:

1) Semiologia das crises: essencial, mas não específica (ou seja, pode ocorrer em ELTM causada por outras etiologias, como por exemplo, tumores de baixo grau)

2) EEG ictal/interictal com distúrbio epileptiforme localizado na região temporal média ou anterior médio-basal: não é essencial, tampouco específico (pode ocorrer em outras formas de epilepsias, por exemplo, epilepsias occipitais, sobretudo em registros de escalpo; porém a semiologia ictal nestes casos geralmente indica uma origem extra-temporal)

3) AH predominantemente unilateral: específica, mas não é essencial (EH discreta pode não ser detectada pela RM)

4) História de insulto precipitante inicial: não é essencial

5) História familiar: não é essencial

6) Período latente: não é essencial

7) Período silente: não é essencial

8) Idade de início das crises: não é essencial, tampouco específica

9) Alteração de memória: não é essencial, tampouco específica

10) Alteração predominantemente unilateral no PET: não é essencial, tampouco específica

11) Resistência às DAEs: não é essencial, tampouco específica

12) Bom prognóstico pós-operatório: não é essencial, tampouco específico

13) Evolução progressiva: não é essencial, mas pode ser específica

Os critérios de exclusão devem ser: aura primariamente sensitiva ou focal motora, atividade epileptiforme extra-temporal, evidência de alteração cerebral difusa e déficits neurológicos focais.

Conclusão: A ELTM associada a EH não é uma doença, mas pode ser uma síndrome (entretanto, é provavelmente um grupo de síndromes distintas), e sendo considerada como tal, está relacionada a múltiplas etiologias (a EH é apenas uma delas). Estudos adicionais precisam ser realizados para a melhor definição da extensão e natureza da patologia estrutural e funcional associada a esta condição.

ELT NEOCORTICAL OU LATERAL (ELTL)

Lesões epileptogênicas localizadas no córtex temporal lateral podem apresentar semiologia indistinta da ELTM quando as crises se propagam rapidamente para a porção medial do lobo temporal. A detecção de uma lesão cortical (por exemplo, um cavernoma) nos exames de imagem facilita o diagnóstico de ELTL. No entanto, o diagnóstico definitivo de ELTL na ausência de uma lesão estrutural é geralmente complexo e sua confirmação definitiva depende de registros ictais invasivos, uma vez que registros de escalpo podem apresentar padrões ictais semelhantes à ELTM. Quando a lesão está próxima ou envolve áreas associativas do lobo temporal (região temporal lateral e superior) a sintomatologia ictal inicial pode se caracterizar por ilusões/alucinações auditivas, ou um bloqueio súbito e precoce da fala ou afasia ictal. Nas lesões localizadas na região temporal posterior e inferior (áreas de associação visual) ocorrem alucinações visuais complexas associadas a movimentos (um objeto que se move de forma estereotipada ou "algo que parece um filme" – geralmente em um quadrante visual). Atividade epileptiforme na região temporal posterior pode ser observada no EEG.

EPILEPSIAS FAMILIARES

Na língua portuguesa, os termos familial e familiar podem ser usados. Segundo alguns [Beigelman B, comunicação pessoal], o termo familiar pode ter uma conotação de "algo conhecido". Portanto, no contexto de doenças com recorrência na família, o termo familial seria mais apropriado. Entretanto, pode-se ainda argumentar que o termo familial, por ser semelhante à grafia na língua inglesa, seria de certa forma um anglicismo.

Decidimos então utilizar neste trabalho de tese, ambos os termos, uma vez que alguns artigos já foram publicados e não houve contestamento da junta editorial no único artigo em língua portuguesa.

Sempre se especulou a respeito da base genética das epilepsias. Hipócrates (400 a.C.) já suspeitava que as epilepsias poderiam ser herdadas e Tissot (1700s) considerava que fatores genéticos resultavam em predisposição para crises epilépticas [Berkovic e Scheffer, 2001]. Estudos epidemiológicos das décadas de 1950 e 1960 demonstraram um risco até cinco vezes maior de desenvolver epilepsia em indivíduos com antecedente familiar da doença em relação à população normal [Andermann, 1982; Treiman, 1989]. Estudos em pares de gêmeos evidenciaram que não somente o fator genético era presente e importante, mas que o modelo de herança envolvido deveria ser não monogênico [Lennox, 1951; Inouye, 1960]. Foi proposto então, um modelo multifatorial para as epilepsias, no qual fatores genéticos e ambientais interagiriam na determinação do fenótipo final [Andermann, 1982].

Apesar do fator genético ser aceito há muito tempo nas epilepsias generalizadas, o mesmo tipo de abordagem nas epilepsias parciais, freqüentemente associadas a causas ambientais, teve início apenas nas últimas décadas. A observação clínica através de estudos de agregação familiar constituiu o passo inicial e foi elemento fundamental para a definição das epilepsias parciais familiares. Tais estudos são consistentes na identificação de um maior risco em familiares de pacientes com epilepsia, na ausência de fatores ambientais lesivos ao sistema nervoso central.

Dentre as epilepsias parciais familiares, podemos identificar a epilepsia de lobo frontal noturna autossômica dominante (com ligação aos cromossomos 20q, 1q e 15q) [Phillips et al., 1995; Steinlein et al., 1995; Steinlein et al., 1997; Phillips et al., 1998], a Epilepsia parcial com foco variável (ligada ao cromossomo 22q) [Xiong et al., 1999], a epilepsia rolândica (cromossomo 15q) [Neubauer et al, 1997], e finalmente as ELT familiares [Berkovic et al., 1996; Cendes et al., 1998].

ELT FAMILIAR

A nova classificação das síndromes epilépticas proposta pela ILAE já inclui algumas epilepsias familiares, entre elas as ELTs [Engel, 2001]. Entretanto, a identificação de antecedente familiar para crises epilépticas em paciente com quadro clínico-eletroencefalográfico de ELT não significa a identificação de uma família com ELT. História de CF e crises isoladas podem ocorrer na população de uma forma geral. Portanto, a avaliação clínica e se possível eletroencefalográfica, de todos os indivíduos possivelmente afetados constitui passo fundamental para a correta classificação das famílias.

Fernandez *et al* [1998] estudaram famílias de pacientes com ELT com antecedente de CF, incluindo RM de indivíduos não afetados. Foram observadas alterações sutis na conformação, estrutura interna e volume dos hipocampos nos pacientes com antecedente de CF e em indivíduos clinicamente não afetados, sugerindo a pré-existência de malformação hipocampal sutil como fator associado ao desenvolvimento de CF e subseqüente AH. Entretanto, o estudo de Jackson *et al* [1998], comparando RM de crianças com CF prolongada e seus gêmeos monozigóticos sem história de crises, não confirmou estes achados [Jackson et al., 1998]. Estudos em gêmeos são métodos importantes para determinar a força da predisposição genética de um caráter ou doença. Por exemplo, uma característica 100% genética deve apresentar uma concordância em 100% dos pares de gêmeos monozigóticos [Smith, 1974]

A presença de indivíduos com diagnóstico clínico-eletroencefalográfico de ELT pode ocorrer em diferentes síndromes epilépticas familiares. Além da ELT familiar, na Epilepsia parcial com focos variáveis podemos encontrar indivíduos com a síndrome clássica de ELT e indivíduos com outras epilepsias parciais.

Caracteristicamente, quando dois ou mais familiares (parentes em primeiro ou segundo graus) preenchem os critérios para ELT, podemos estar diante de dois tipos distintos de ELT familiar. Na ELTMfamiliar, a semiologia das crises é compatível com origem nas regiões mesiais temporais e suas características, assim como os achados do EEG, são semelhantes aos encontrados em pacientes com ELTM sem história familiar de crises. Quando há relato de fenômenos como zumbidos, alteração da percepção de sons ou

linguagem, trata-se da ELTLfamiliar (ou epilepsia parcial autossômica dominante com auras auditivas).

Inicialmente descrita como benigna, a ELT familiar vem sendo intensamente investigada, tanto no que se refere à apresentação clínica quanto às alterações em RM. O primeiro relato de ELT familiar foi a partir de estudo em gêmeos, e demonstrou um caráter benigno e início tardio de crises, além de investigação por RM normal [Berkovic et al., 1996].

Em seguida, outra série de ELT familiar foi descrita [Cendes et al., 1998], sendo incluídos apenas pacientes com a forma mesial de ELT (ELTMfamiliar). Onze famílias não relacionadas com 36 indivíduos afetados foram estudadas, sendo observado um padrão variável em termos de severidade das crises, inter e intrafamiliar, com casos refratários (inclusive cirúrgicos), apesar da maioria apresentar bom controle medicamentoso ou remissão espontânea das crises. RM com padrão sugestivo de AH foi observada em 61% dos pacientes, com diferentes graus de atrofia, sugerindo um fator genético envolvido no desenvolvimento da patologia hipocampal em pacientes com ELTMfamiliar.

Uma forma bastante peculiar de ELT familiar é a ELT com auras auditivas ligada ao cromossomo 10q [Ottman et al., 1995; Poza et al., 1999], cujo gene foi recentemente clonado (*leucine-rich, glioma-inactivated 1 gene* -LGI1) [Kalachikov et al., 2002; Morante-Redolat et al., 2002]. Trata-se de uma forma benigna de ELT familiar, com crises caracterizadas por fenômenos auditivos tipo zumbidos/ ruídos, ou afasia ictal, com atividade epileptiforme na região temporal posterior e RM aparentemente normal. Os pacientes descritos até o momento apresentam evolução clínica favorável com controle total de crises com medicamentos ou remissão espontânea.

CAPÍTULO 2

OBJETIVOS E METODOLOGIA

OBJETIVOS

Os objetivos deste estudo foram:

1) Determinar o padrão clínico dos pacientes com ELT familiar em nosso meio: idade de início das crises, identificação de fatores de risco (convulsão febril, trauma cranioencefálico, meningite), tipos de crises, história natural da epilepsia, necessidade de tratamento cirúrgico, resposta à cirurgia, variação intra e interfamiliar.

2) Estudar através de RM a presença de AH ou outras anormalidades hipocampais nos indivíduos afetados (avaliação qualitativa e quantitativa).

3) Estudar as alterações eletroencefalográficas nesses indivíduos.

4) Correlacionar os achados de RM com a apresentação clínica

5) Investigar familiares clinicamente assintomáticos através de RM.

METODOLOGIA

Aspectos éticos

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP (anexo1), e oferece riscos mínimos aos pacientes e seus familiares. O estudo faz parte de outros projetos temáticos, para estudo de neuroimagem e genética molecular em epilepsias, também aprovados pelo comitê de ética e com suporte científico e financeiro da FAPESP.

Todos os indivíduos participantes deste estudo foram devidamente esclarecidos quanto às finalidades da pesquisa, através de formulários de consentimento informado (anexos 2 e 3).

Identificação dos indivíduos e famílias

Todos os pacientes com diagnóstico de ELT em seguimento ambulatorial no Hospital das Clínicas da UNICAMP foram questionados sobre antecedente familiar de eventos paroxísticos que pudessem sugerir crises epilépticas. Solicitamos a todos os pacientes que verificassem com familiares de maior idade a ocorrência de crises na família, preferencialmente a mãe ou a avó.

Todos aqueles com suspeita de história positiva foram convidados a participar do estudo, que inicialmente incluiu entrevista com os demais familiares e obtenção de um heredograma detalhado. Quando a história de crises nos outros familiares não podia ser devidamente esclarecida, estes foram considerados possivelmente afetados.

Definição de ELT E ELT familiar

ELT familiar foi definida quando havia recorrência familiar de ELT, em critérios práticos quando dois ou mais indivíduos (parentes em primeiro ou segundo grau) apresentavam quadro de crises parciais recorrentes, semiologicamente compatíveis com crises de lobo temporal, na ausência de elementos neurofisiológicos que sugerissem epilepsia extratemporal. Dois tipos de ELT familiar foram reconhecidos, ELTMfamiliar e ELTLfamiliar, conforme a semiologia das crises.

As crises e síndromes epilépticas foram definidas de acordo com a classificação da ILAE [Comission on classification and terminology of the ILAE, 1981; 1989], através de interrogatório detalhado com o paciente e testemunha das crises.

Classificação clínica dos indivíduos

Todos os indivíduos com história de crises epilépticas e devidamente avaliados foram considerados clinicamente afetados. Os indivíduos com história de crise, mas que não preenchiam critérios para diagnóstico de ELT, foram também incluídos desde que fizessem parte de uma família com dois outros indivíduos afetados com diagnóstico de ELT.

Aqueles com quadro clínico-eletroencefalográfico de ELT foram divididos ainda conforme o controle de crises em:

- evolução benigna (ELT familiar benigna): crises com bom controle medicamentoso (até 3 CPC/ano ou crises relacionadas à falta de medicação) ou remissão por pelo menos 2 anos.

- crises refratárias ao tratamento clínico (ELT familiar refratária), com uso prévio de pelo menos duas monoterapias e uma politerapia.

Os indivíduos que não preenchiam critérios para ELT, com outros tipos de crises apresentavam:

- CTCG sem início parcial identificável por história ou observação clínica.

- crise febril (única ou recorrente), definida como simples (menor de 15 minutos de duração, sem início parcial, único episódio em 24 horas do quadro febril) ou complexa (maior de 15 minutos de duração, com início parcial, recorrente em 24 horas).

- crise única (com ou sem início parcial identificável).

Indivíduos com história de crises, porém não avaliados (sem esclarecimento da síndrome epiléptica), foram classificados como possivelmente afetados, desde que pertencentes a uma família com pelo menos dois outros indivíduos com diagnóstico comprovado de ELT.

Critérios de exclusão

Foram excluídas famílias em que: 1) apenas um indivíduo pôde ser classificado como ELT, independentemente do número de outros familiares com história de crises; 2) apesar de apresentar dois indivíduos com quadro clínico compatível com ELT o exame de RM e/ou de EEG sugerir outra síndrome epiléptica; 3) pacientes com antecedente familiar positivo mas com todos os indivíduos possivelmente afetados não disponíveis para avaliação clínica; 4) famílias com dois ou mais indivíduos com critérios clínico-

eletroencefalográfico para ELT, porém parentes em terceiro ou mais graus, independente do número de familiares mais próximos com outros tipos de crises; 5) suspeita de epilepsia parcial extra-temporal em algum familiar próximo afetado.

Avaliação eletroencefalográfica

Todos os indivíduos avaliados foram convidados a realizar exame de EEG. Utilizamos aparelhos de 16 canais e sistema 10-20 de colocação de eletrodos para registro analógico ou digital, com duração aproximada de 30 minutos, seguindo o protocolo de rotina do serviço.

Os pacientes com crises refratárias foram ainda submetidos a monitorização por vídeo-EEG, como parte da investigação clínica rotineira destes pacientes, não sendo exclusiva para este estudo.

Investigação com ressonância magnética

Todos os indivíduos afetados e possivelmente afetados, bem como assintomáticos (parentes em primeiro grau) foram convidados para realização de exame de RM de alta resolução. Os exames foram realizados após assinatura de termo de consentimento para pesquisa (anexos 2 e 3).

As imagens foram obtidas em um sistema de 2 T (Elscint Prestige®), com aquisições nos planos coronal, sagital e axial, além de aquisição em 3D (volumétrica), para reconstrução multiplanar. Os parâmetros de imagem para as diferentes aquisições foram:

1. Imagens sagitais T1 ponderadas "spin echo"(espessura de 6mm, ângulo de excitação – "tip angle"- de 180° ; TR=430, TE=12, matriz de 200X350, FOV=25X25cm). Estas imagens são utilizadas para orientar o plano de aquisição das demais imagens.

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

a) T2 ponderadas "fast spin echo" (espessura de 3 a 4mm, ângulo de excitação de 120°; TR=4800, TE=129, matriz de 252X320, FOV=18X18cm).

b) T1 ponderadas "inversion recovery" (espessura de 3mm, ângulo de excitação de 200°; TR=2800, TE=14, TI=840, matriz de 130X256, FOV=16X18cm).

3. Imagens no plano axial: "duplo spin echo"(T2 ponderadas e densidade de prótons): T2 ponderadas (espessura de 6mm, ângulo de excitação de 180°; TR=1800, TE=90, matriz de 165X256, FOV=20X24cm) ou "fast spin echo"T2 ponderadas (espessura de 4mm, ângulo de excitação de 120°, TR=6800, TE=129, matriz de 252X328, FOV=21X23cm).

4. Aquisição 3D obtida no plano sagital "gradient echo" T1 ponderadas (espessura de 1 a 1,5mm, ângulo de excitação de 35°, TR=22, TE=9, matriz de 256X220, FOV=230X250cm, pixel=1X1).

Análise qualitativa das imagens foi realizada em estação de trabalho (OMNIPRO®). Avaliamos características de forma, assimetria e dimensões dos hipocampos, além de evidências de alteração na estrutura interna e sinal. Além disso, a presença de outras alterações fora das regiões mediais do lobo temporal, também foram contempladas.

Análise quantitativa com volumetria dos hipocampos foi realizada utilizando as seqüências de cortes coronais T1-IR, através do programa NIH Image®, obtido da INTERNET (http://www. rsb.info.nih.gov/nih-image). Os parâmetros anatômicos utilizados para o estudo volumétrico são os descritos em protocolos publicados previamente [Cendes et al, 1993b; Watson et al, 1992; Watson et al ,1997].

Apresentação e análise dos dados

Os dados referentes à investigação das famílias estão apresentados sob a forma de artigos, com enfoque específico a cada aspecto da avaliação, cujos resultados estão dispostos no capítulo III.

Assim, a epidemiologia geral das epilepsias parciais familiares no ambulatório do HC UNICAMP foi descrita no artigo #1; a partir deste estudo preliminar, identificamos aquelas famílias com ELTMfamiliar e ELTLfamiliar. A descrição

clínico-eletroencefalográfica, bem como da análise visual de RM, das famílias com ELTM encontra-se no artigo #2. Estudo volumétrico e análise qualitativa do sinal T2 hipocampal em pacientes com ELTMfamiliar está relatado no artigo #3, enquanto o artigo #4 aborda este mesmo aspecto nos familiares assintomáticos. No artigo #5, descrevemos a investigação pré-cirúrgica, evolução pós-operatória e patologia hipocampal em pacientes com ELTM familiar refratária que foram submetidos a tratamento cirúrgico. Aspectos da avaliação neuropsicológica de pacientes com ELTMfamiliar são discutidos no artigo #6. Avaliação de alterações mais difusas nos lobos temporais dos pacientes com ELTMfamiliar foi realizada e descrita no artigo #7. No artigo #8, descrevemos os achados de neuroimagem em uma grande família com a forma lateral de ELT (ELTLfamiliar).

Para fins ilustrativos das famílias avaliadas, os heredogramas podem ser contemplados no anexo 4.

CAPÍTULO 3

RESULTADOS

(Artigos publicados no prelo e submetidos para publicação)

Artigo 1

Epilepsias parciais familiares

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EPILEPSIAS PARCIAIS FAMILIARES

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RESUMO - *Objetivo:* Investigação das características clínicas e genéticas das epilepsias parciais familiares nos ambulatórios de epilepsia da UNICAMP. *Método:* História familiar foi obtida em todos os pacientes em acompanhamento, de outubro de 1997 a dezembro de 1998, e aqueles com história familiar positiva para epilepsia foram investigados em detalhe. Heredograma detalhado foi construído para todas as famílias identificadas e história clínica de todos os indivíduos possivelmente afetados foi obtida. Crises e síndromes epilépticas foram classificadas de acordo com as recomendações da ILAE. Sempre que possível, EEG e ressonância magnética foram realizados. *Resultados:* História familiar positiva foi identificada em 32 pacientes não relacionados. Um total de 213 indivíduos possivelmente afetados foram identificados, dos quais 161 foram clinicamente avaliados. O número de indivíduos afetados por família variou de dois a 23. Epilepsia de lobo temporal (ELT) foi identificada em 22 famílias (68%), epilepsia de lobo frontal em uma família (3%), epilepsia com espículas centro-temporais em cinco famílias (15%) e outras epilepsias parciais benignas da infância em quatro famílias (12%). A maioria dos indivíduos afetados nas famílias com ELT (69%) apresentava características clínicas e/ou de EEG consistentes com ELT típica. Entretanto, a gravidade da epilepsia variou, com 76% dos pacientes com remissão de crises ou bom controle com medicação, e 24% com crises refratárias, incluindo 7 pacientes que foram submetidos a tratamento cirúrgico. Nas 10 famílias com outras síndromes epilépticas, identificamos 39 indivíduos possivelmente afetados, sendo 23 avaliados clinicamente. Todos apresentavam bom controle de crises (com ou sem medicação) exceto um paciente com epilepsia frontal. Análise dos heredogramas sugeriu herança autossômica dominante com penetrância incompleta em todas as famílias estudadas. *Conclusão:* A ocorrência familiar é comum nas epilepsias parciais, tanto em adultos como em crianças. A maior parte dos casos estudados foi de pacientes com ELT e a expressão clínica não foi diferente da observada em casos esporádicos, predominando pacientes com bom controle de crises, apesar do caráter heterogêneo. A identificação dos genes envolvidos nos casos estudados poderá ser útil na classificação das síndromes epilépticas, na determinação do prognóstico e regime terapêutico mais indicado.

PALAVRAS-CHAVE: epilepsia parcial, genética, recorrência familiar, epilepsia do lobo temporal.

Familial partial epilepsies

ABSTRACT - *Objective:* To investigate the clinical and genetic characteristics of familial partial epilepsies. *Method:* Family history of seizures was questioned in all patients followed in our epilepsy clinics, from October 1997 to December 1998. Those with positive family history were further investigated and detailed pedigrees were obtained. All possibly affected individuals available underwent clinical evaluation. Seizures and epilepsy syndromes were classified according to the ILAE recommendations. Whenever possible, EEG and MRI were performed. *Results:* Positive family history was identified in 32 unrelated patients. A total of 213 possibly affected individuals were identified, 161 of whom have been evaluated. The number of affected subjects per family ranged from two to 23. Temporal lobe epilepsy (TLE) was identified in 22 families (68%), frontal lobe epilepsy in one family (3%), partial epilepsy with centrotemporal spikes in five families (15%), and other benign partial epilepsies of childhood in four families (12%). Most of the affected individuals in the TLE families (69%) had

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clinical and/or EEG characteristics of typical TLE. However, the severity of epilepsy was variable, with 76% of patients with spontaneous seizure remission or good control with medication and 24% with refractory seizures, including 7 patients that underwent surgical treatment. In the other 10 families, we identified 39 possibly affected subjects, 23 of whom were evaluated. All had good seizure control (with or without medication) except for one patient with frontal lobe epilepsy. Pedigree analysis suggested autosomal dominant inheritance with incomplete penetrance in all families. *Conclusion:* Family history of seizures is frequent among patients with partial epilepsies. The majority of our families had TLE and its expression was not different from that observed in sporadic cases. The identification of genes involved in partial epilepsies may be usefull in classification of syndromes, to stablish prognosis and optimal treatment.

KEY WORDS: partial epilepsy, genetics, familial recurrence, temporal lobe epilepsy.

A influência de fatores genéticos nas epilepsias sempre foi suspeitada, sendo que a recorrência familiar foi inicialmente demostrada nas epilepsias generalizadas[1-5] e mais recentemente também nas epilepsias parciais[6-11]. Clinicamente, muitas destas síndromes se apresentam de forma heterogênea, o que pode dificultar o reconhecimento da recorrência familiar. Nas epilepsias parciais com apresentação benigna, muitos pacientes podem não ser corretamente diagnosticados ou simplesmente não ser do conhecimento do restante da família a ocorrência remota de algum episódio compatível com crise epiléptica.

Vários estudos de genética molecular estão em andamento, visando à localização do defeito específico nas várias síndromes. Até o momento pelo menos 18 loci já foram mapeados nas epilepsias idiopáticas. Quatro genes foram identificados, sendo todos relacionados a subunidades de canais iônicos[12-15]. A identificação de um maior número de famílias pode contribuir para que estes estudos esclareçam as bases moleculares das epilepsias e permitam não somente melhor correlação clínica como o desenvolvimento de novas perspectivas terapêuticas.

Os objetivos deste estudo são: estimar a ocorrência de epilepsias parciais familiares em nosso meio e descrever as características clínicas e genéticas dos casos familiares identificados.

MÉTODO

História familiar foi sistematicamente pesquisada em todos os pacientes acompanhados nos ambulatórios de epilepsia do Hospital das Clínicas da UNICAMP (HC-UNICAMP) a partir de outubro de 1997. Aqueles com história positiva foram posteriormente investigados.

História clínica detalhada e heredograma foram obtidos para todas as famílias identificadas. Crises e síndromes epilépticas foram classificadas de acordo com as recomendações da International League Against Epilepsy (ILAE)[16].

Foram classificadas como epilepsias parciais aquelas em que a semiologia das crises claramente pudesse ser identificada como crise parcial, com ou sem generalização secundária, em pelo menos um indivíduo. EEG normal ou com atividade epileptiforme generalizada não excluiu o diagnóstico de epilepsia parcial desde que as crises pudessem ser claramente identificadas como crises parciais. Conforme a manifestação clínica, foram subdivididas em: epilepsia de lobo temporal (ELT), epilepsia de lobo frontal (ELF) e epilepsias parciais benignas da infância (EPBI). As EPBI foram assim classificadas, conforme os critérios de Aicardi[17].

Sempre que possível, registro do eletrencefalograma (EEG) e ressonância magnética (RM) foram realizados, com ênfase nos pacientes com ELT e com controle insatisfatório de crises. Todos os pacientes foram devidamente informados dos objetivos da pesquisa e consentimento pós-informação foi obtido.

RESULTADOS

Foram identificadas 32 famílias não relacionadas (Tabela 1) com pelo menos dois indivíduos com crises epilépticas compatíveis com epilepsia parcial, num total de 210 indivíduos possivelmente afetados. Desses, avaliamos clinicamente 161 indivíduos.

Epilepsia de lobo temporal (ELT) foi a síndrome epiléptica mais frequentemente encontrada (Tabela 2), num total de 22 famílias e 121 indivíduos possivelmente afetados (dois a 22 por família,

Tabela 1. 32 famílias com epilepsia parcial.

	Epilepsia de lobo frontal	Epilepsia de lobo temporal	Epilepsia com espículas centro temporais	Outras epilepsias parciais benignas
Nº de famílias	1	22	5	4
Nº de pacientes avaliados	4	98	11	7
Nº de pacientes com crises refratárias	1	16	0	0

Tabela 2. Características clínicas em 22 famílias com ELT (98 indivíduos avaliados).

ELT com remissão	ELT com bom controle medicamentoso	ELT refratária	Apenas CTCG	Apenas CF	Crise única
15 (22%)	37 (54%)	16 (24%)	11 (11%)	11 (11%)	8 (8%): 5 parcial 3 CTCG

ELT, epilepsia de lobo temporal; CTCG, crises tônico-clônicas generalizadas; CF, convulsão febril.

média de cinco indivíduos por família). Destes, 98 foram avaliados, sendo 46 homens e 52 mulheres. A idade de início de crises variou de três meses a 35 anos (média= nove anos). Sessenta e oito pacientes apresentavam quadro clínico típico de ELT, com diferentes graus de gravidade (22% com remissão de crises há pelo menos dois anos, 54% com bom controle medicamentoso e 24% com crises refratárias). Sete pacientes necessitaram de tratamento cirúrgico. Onze pacientes tiveram apenas crises tônico-clônicas generalizadas (CTCG) que não puderam ter um início parcial identificado, todos com remissão de crises há vários anos. Onze pacientes apresentaram apenas convulsões febris (CF): recorrentes em cinco pacientes e única em sete pacientes. Oito pacientes apresentaram uma única crise (parcial em cinco e CTCG em três pacientes).

Entre os 68 pacientes com ELT, 57 (85%) apresentaram crises parciais simples (CPS), mais frequentemente do tipo autonômica. Crise parcial complexa (CPC) foi referida por 62 (92%) pacientes e CTCG secundária ocorreu em 57 (85%), principalmente no início da epilepsia.

Sessenta e quatro pacientes realizaram EEG, que evidenciou alteração epileptiforme em regiões temporais em 27 indivíduos (42%) (Fig 1A). Sete pacientes com crises refratárias foram submetidos à monitorização vídeo-EEG, todos com registro de crises nas regiões temporais (Fig 1B). RM foi realizada em 84 pacientes, sendo identificada alteração hipocampal em 49 pacientes (58%): 45 com atrofia hipocampal (AH) (Fig 2) e quatro com alteração de eixo ou formato do hipocampo.

Epilepsia frontal (ELF) foi identificada em uma família, com sete indivíduos possivelmente afetados, dos quais quatro foram avaliados (idade atual de 14 a 55 anos, média 34). A idade de início das crises variou de sete a 44 anos (média 21 anos). As características semiológicas das crises foram compatíveis com CP em dois indivíduos e CTCG sem início parcial identificável em dois indivíduos. Todos, exceto um paciente, apresentaram evolução benigna, com remissão de crises em um paciente e crise única no outro. EEG foi realizado em dois pacientes, normal em um deles e com atividade epileptiforme em um paciente. Este paciente também foi submetido a monitorização vídeo-EEG, sendo registradas crises de início frontal bilateral com predomínio à direita (Fig 1C). Este paciente apresenta RM normal à análise visual.

Epilepsia parcial benigna da infância (EPBI) foi identificada em nove famílias. - Epilepsia com espículas centro-temporais (EECT) ocorreu em cinco famílias, com 16 indivíduos possivelmente

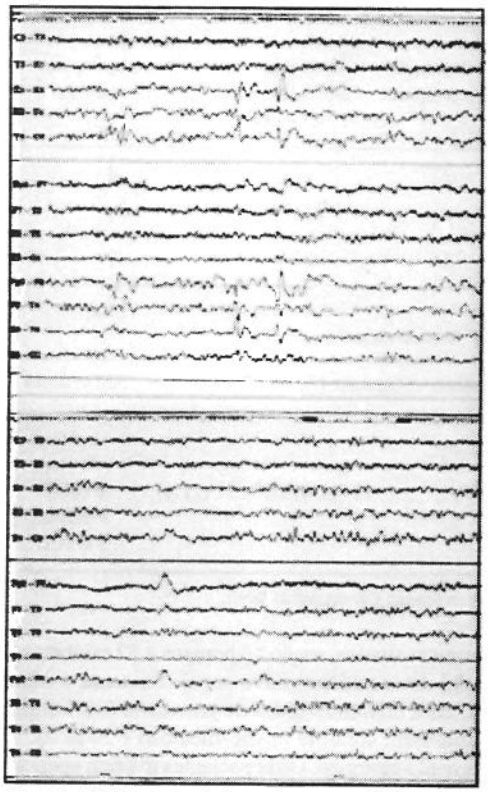

Fig 1A. EEG interictal de paciente com ELT e crises refratárias e RM com atrofia hipocampal direita. O traçado mostra espículas, ondas agudas e ondas lentas intermitentes na região temporal anterior e mediobasal direita.

afetados (máximo de seis indivíduos por família). Destes, 11 (69%) foram avaliados (oito homens e três mulheres) com idade variando entre oito e 67 anos (média de 25 anos). O início das crises ocorreu entre três e 16 anos (média= nove anos) e todos apresentaram boa evolução, com crises controladas ou em remissão há pelo menos dois anos. Seis indivíduos realizaram EEG, sendo normal em cinco e com espículas centro-temporais em um indivíduo. Seis pacientes realizaram TC de crânio, sendo todas normais.

- Epilepsia parcial benigna da infância com paroxismos occipitais (EPPO) foi identificada em duas famílias, com oito indivíduos possivelmente afetados. Três pacientes foram avaliados, com idade média atual de 20 anos (variando de sete a 38 anos). Idade de início das crise foi de dois a cinco anos. Apenas um paciente não apresentou sintomas visuais no início das crises. Dois pacientes realizaram EEG e apenas um mostrou atividade epileptiforme.

- Epilepsia parcial benigna da infância que não pôde ser classificada nos grupos anteriores foi identificada em duas famílias. Os tipos de crises identificados foram: sensitiva em dois pacientes, motora em um paciente e visual em quatro pacientes. Um paciente teve uma única crise febril e um paciente teve uma única CTCG sem início parcial identificável. A evolução foi benigna em todos os pacientes, sendo que a maioria deles apresentou apenas dois ou três episódios durante a vida.

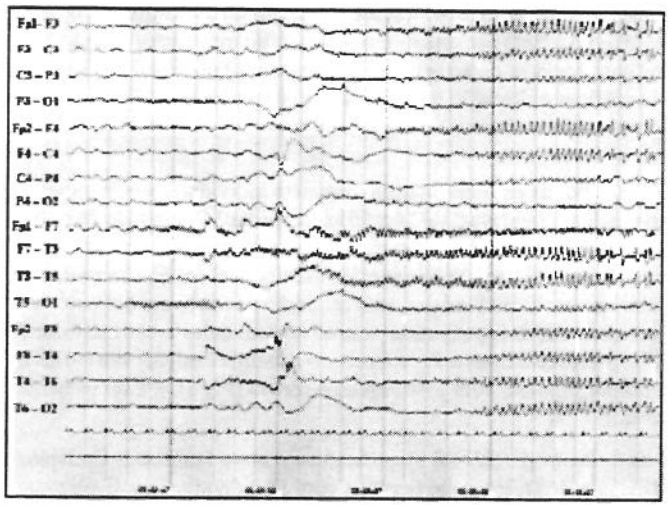

Fig 1B. EEG ictal de paciente com ELT crises refratárias, com início eletrográfico na região temporal esquerda. Apresentava atrofia hipocampal esquerda à RM e foi submetido a ressecção temporal envolvendo amígdala e hipocampo (classe IIa de Engel após 25 meses de seguimento).

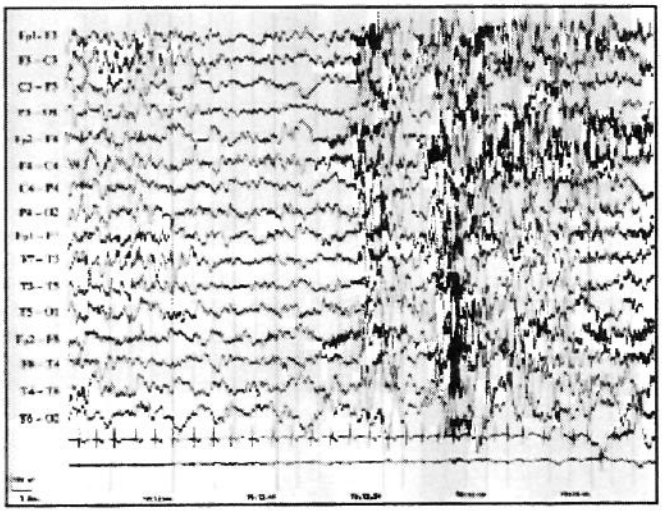

Fig 1C. Registro ictal de crise de início bifrontal com predomínio à direita (reversão de fase em F4) no único paciente com quadro refratário de epilepsia de lobo frontal (RM normal à análise visual).

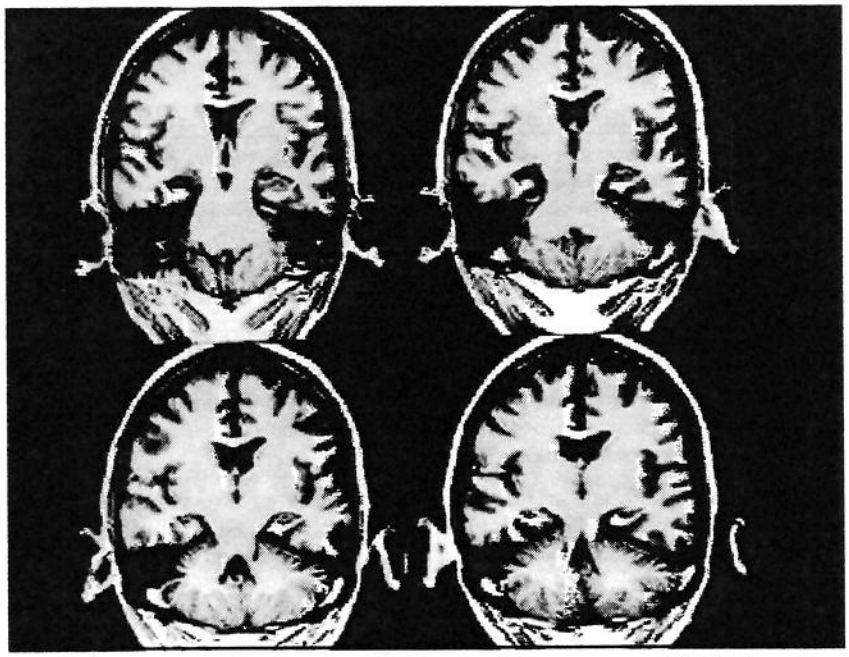

Fig 2. RM de paciente com ELT e crises refratárias (irmã da paciente cujo EEG foi ilustrado na figura 1A), em cortes coronais Inversion Recovery, *mostrando atrofia hipocampal direita.*

Análise dos heredogramas sugeriu padrão de herança autossômica dominante com penetrância incompleta em todas as famílias identificadas (Fig 3). É interessante notar a grande frequência de história familiar de epilepsia presente em ambos os lados paterno e materno de várias famílias.

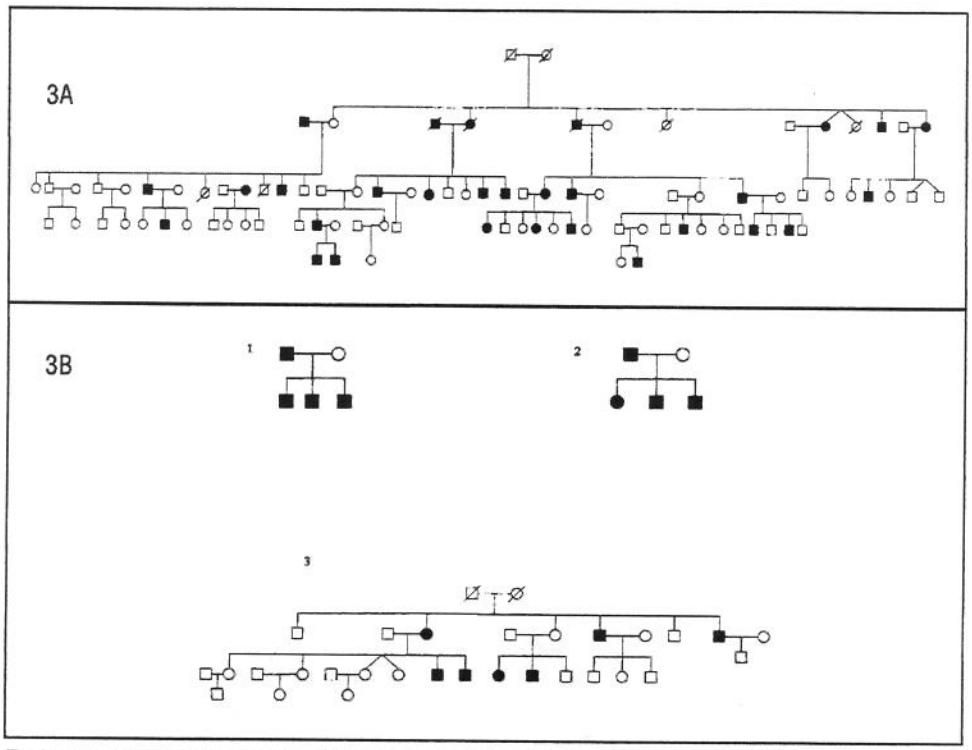

Fig 3. Heredogramas de quatro famílias com epilepsia parcial: 3A, família com ELT; 3B, famílias com epilepsia parcial benigna com espículas centrotemporais. (1), epilepsia parcial benigna da infância (2) e epilepsia frontal (3). ■ ● Indivíduo com pelo menos uma crise febril ou afebril; □ ○ Indivíduo não afetado; ⊠ ∅ Indivíduo falecido.

DISCUSSÃO

Nosso grupo de pacientes foi constituído em sua maior parte por famílias com ELT. Não podemos descartar a possibilidade de um viés na população estudada, uma vez que os pacientes que frequentam os ambulatórios de epilepsia do HC-UNICAMP são encaminhados de outros serviços de atendimento, primários e secundários. Portanto, muitos casos de epilepsia benigna e de fácil controle não são rotineiramente avaliados pela nossa equipe.

Entretanto, mesmo em nossa amostragem "selecionada", conseguimos identificar casos familiares de epilepsias parciais benignas. Muitos pacientes não sabiam relatar num primeiro questionamento a ocorrência de crises em seus familiares, em geral pela extrema benignidade dos episódios.

A única família identificada com epilepsia frontal apresenta um único indivíduo com crises refratárias noturnas, compatível com quadro de epilepsia frontal familiar previamente descrito[7]. Dentre os pacientes com ELT, pudemos observar heterogeneidade importante intra e interfamiliar, semelhante a observações de outra série previamente publicada[10].

Acredita-se que a real prevalência das epilepsias parciais familiares seja subestimada, principalmente devido à dificuldade de obtenção de informação relativa aos antecedentes familiares e de seleção e classificação dos indivíduos afetados. Interrogatório sistemático e ativo em todos os pacientes avaliados pode auxiliar na identificação de um número maior de famílias, permitindo um estudo clínico mais detalhado em nosso meio. Além disso, o estudo da população atendida em

serviços primários e secundários de saúde, principalmente na faixa pediátrica, pode fornecer dados epidemiológicos mais representativos.

A importância do reconhecimento e estudo das epilepsias parciais familiares está relacionada à perspectiva de se aprofundar nos mecanismos moleculares provavelmente envolvidos na epileptogênese que possibilitarão o desenvolvimento de novas estratégias terapêuticas no futuro.

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Artigo 2

Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy

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Neurology 2001;56(2):166-172

CME

Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy

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Article abstract—*Objective:* To describe the clinical, genetic and MR characteristics of patients with familial mesial temporal lobe epilepsy (MTLE). *Design/Methods:* The familial occurrence of MTLE was identified by a systematic search of family history of seizures in patients followed in the authors' epilepsy clinic. All probands and, whenever possible, other affected family members underwent EEG and MR investigations. *Results:* Twenty-two unrelated families with at least two individuals with MTLE were identified by clinical and EEG findings. Ninety-eight individuals with history of seizures were evaluated. Sixty-eight patients fulfilled the diagnostic criteria for MTLE. MRI was performed in 84 patients, and showed hippocampal atrophy with increased T2 signal in 48 (57%). The distribution of hippocampal atrophy according to the seizure outcome groups was 6 of 13 patients (46%) with seizure remission, 16 of 31 (51%) with good seizure control under medication, and all 16 patients with refractory MTLE. Hippocampal atrophy was found also in patients that did not fulfill the criteria for MTLE: 3 of 10 (30%) patients with febrile seizure alone, 6 of 10 (60%) patients with recurrent generalized tonic-clonic seizures, and 1 of 4 (25%) patients with a single partial seizure. *Conclusion:* Familial MTLE is a clinically heterogeneous syndrome. Hippocampal atrophy was observed in 57% of patients, including those with benign course or seizure remission, indicating that the relationship between hippocampal atrophy and severity of epilepsy might be more complex than previously suspected. In addition, these findings indicate the presence of a strong genetic component determining the development of mesial temporal sclerosis in these families.

NEUROLOGY 2001;56:166–172

The relationship between mesial temporal lobe epilepsy (MTLE) and hippocampal pathology has been recognized since the first pathologic report of a severe neuron loss in Sommer's sector (CA1 and prosubiculum) and the end folium (hilus and CA4), with CA3 and CA2 being somewhat spared from damage.[1] The neuron loss may also involve the amygdala and parahippocampal gyrus, characterizing the typical pattern of mesial temporal sclerosis (MTS). Development of high-resolution MRI allowed in vivo diagnosis in patients with MTS and its correlation with pathology and other clinical data.[2-4] Genetic factors seem to play a role in patients with MTS and history of febrile seizures, as there is a high prevalence of febrile seizures and epilepsy in the families of these patients.[5] However, the exact relationship among familial forms of MTLE, MTS, and antecedent of febrile seizure has not been clarified yet.

In the current study, we report 22 unrelated families with MTLE identified in at least two affected individuals.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the January 23 issue to find the title link for this article.

Patients and methods. *Ascertainment of subjects.* We questioned patients with MTLE in our epilepsy clinic regarding family history of epilepsy. We obtained pedigrees, medical history, and neurologic examination in families in which one or more individuals had suspected MTLE. All participating individuals gave informed consent. This study was approved by the Ethics Committee of the UNICAMP Medical School.

Familial MTLE was defined when two or more individuals presented with the diagnosis of MTLE. Additional family members who had seizures but who did not fulfill the criteria for MTLE were analyzed separately.

The diagnosis of MTLE was based on clinical and EEG findings.[6] Clinical criteria were history of simple partial seizures or complex partial seizures or both, with characteristics compatible with mesial temporal lobe origin (in general, rising epigastric sensation, fear, experiential phenomena, and autonomic signs and symptoms)[7] and no suggestion of other partial epilepsy syndrome. EEG criteria were presence of interictal epileptiform discharges over midinferomesial temporal regions or consistent intermittent slow wave abnormalities with episodes of rhythmic

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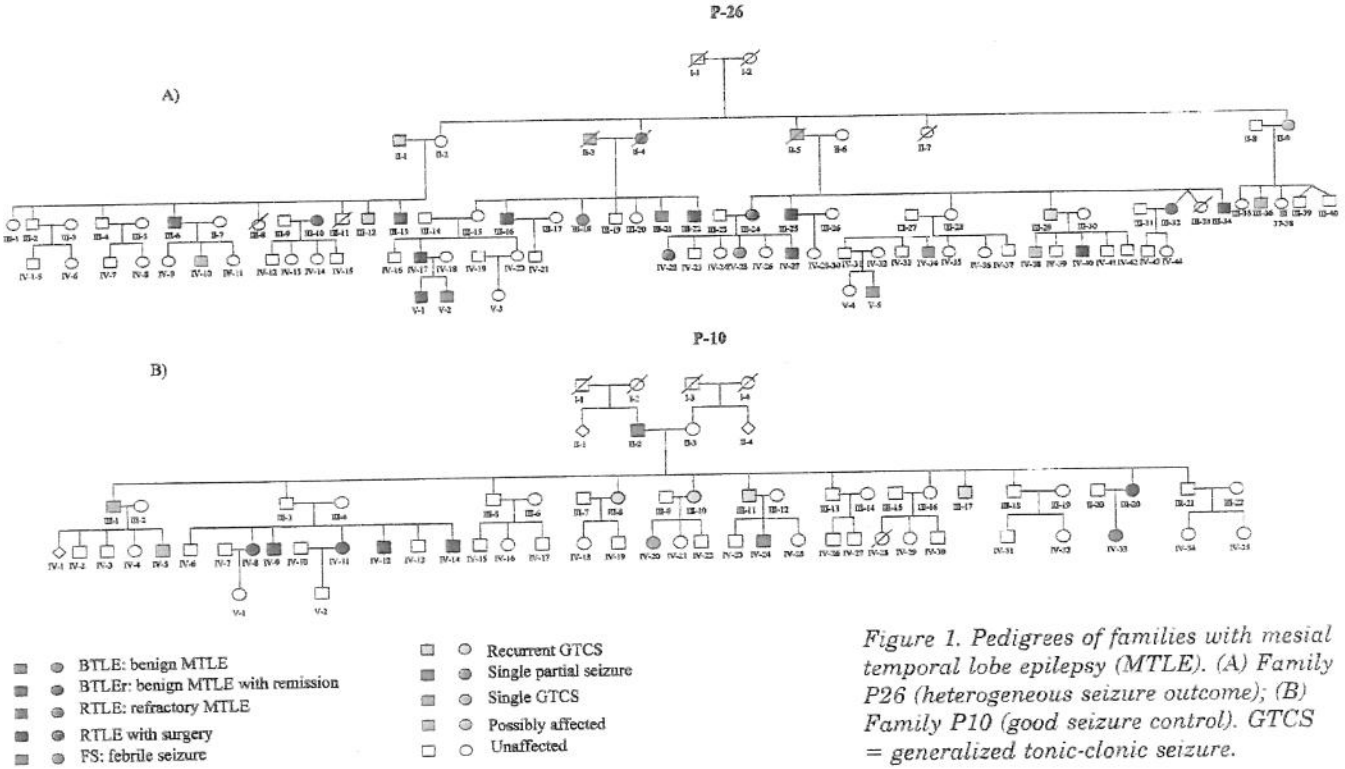

Figure 1. Pedigrees of families with mesial temporal lobe epilepsy (MTLE). (A) Family P26 (heterogeneous seizure outcome); (B) Family P10 (good seizure control). GTCS = generalized tonic-clonic seizure.

delta activity localized over the temporal areas and noclear-cut epileptiform abnormalities elsewhere. Normal interictal EEG did not exclude the diagnosis of MTLE. Any suggestion of lateral temporal lobe epilepsy by seizure semiology and EEG findings were exclusion criteria. These criteria included auditory or visual auras and interictal or ictal EEG epileptiform abnormalities over the posterior temporal regions. The presence of hippocampal atrophy and other abnormalities compatible with MTS was analyzed independently of the clinical diagnosis of MTLE.

Clinical classification. Patients who fulfilled the clinical criteria for MTLE were divided into three groups, according to seizure outcome: 1) remission—seizure-free for at least 2 years, off medication; 2) good seizure control—patients on medication, with less than six complex partial seizures per year and no more than two secondary generalized tonic-clonic seizures per year; 3) refractory MTLE—poor outcome with medically refractory seizures.

In addition, families were classified into three groups, according to clinical characteristics of the affected subjects: 1) families with benign MTLE—patients in remission or with good seizure control; 2) families with severe MTLE—only refractory patients; 3) families with heterogeneous seizure outcome—patients with benign and severe MTLE.

EEG recordings. Interictal EEG recordings were performed routinely, using the International 10–20 System for electrode placement. Seven patients with refractory seizures also had ictal video-EEG studies.

MR studies. All MR scans were obtained in a 2 T scanner (Elscint Prestige, Haifa, Israel). We performed T1- and T2- weighted MRI in three orthogonal planes as well as thin coronal T1 inversion recovery (IR) images perpendicular to the long axis of the hippocampus to optimize the evaluation of mesial temporal structures.

MR acquisition parameters were as follows: 1) sagittal T1 spin echo, 6 mm thick, flip angle = 180°, repetition time (TR) = 430 ms, echo time (TE) = 12 ms, matrix = 200 × 350, field of view (FOV) = 25 × 25 cm; 2) coronal images, perpendicular to long axis of hippocampus, defined by the sagittal images: (a) T2-weighted fast spin echo (FSE), 4 mm thick, flip angle = 120°, TR = 4,800 ms, TE = 129 ms, matrix = 252 × 320, FOV = 18 × 18 cm; (b) T1-weighted IR, 3 mm thick, flip angle = 200°, TR = 2,800–3,000 ms, TE = 14 ms, inversion time = 840 ms, matrix = 130 × 256, FOV = 16 × 18 cm; 3) axial images parallel to the long axis of the hippocampi: (a) T1-weighted gradient echo, 3 mm thick, flip angle = 70°, TR = 200 ms, TE = 5 ms, matrix = 180 × 232, FOV = 22 × 22 cm; (b) T2-weighted FSE, 4 mm thick, flip angle = 120°, TR = 6,800 ms, TE = 129 ms, matrix = 252 × 328, FOV = 21 × 23 cm; 4) T1-weighted three-dimensional gradient echo, acquired in the sagittal plane for multiplanar reconstruction, 1.5 mm thick, flip angle = 35°, TR = 22 ms, TE = 9 ms, matrix = 256 × 220, FOV = 23 × 25 cm.

Qualitative analysis was performed independently of clinical and EEG data, with particular attention to asymmetry of the hippocampi, altered shape and size, abnormal internal structure with increased T2 signal, and abnormal spatial orientation of hippocampus. In addition, a multiplanar reconstruction analysis was performed when visual analysis of conventional orthogonal MR images did not show clear-cut abnormalities.

Results. From October 1997 to June 1999, we identified 29 unrelated probands with MTLE and family history of seizures, among the ≈400 patients with all clinical forms of TLE evaluated in our epilepsy clinic during this period. Therefore, the estimated frequency of positive family history in MTLE in our clinic was 7%. In 22 families, we were able to identify two or more subjects with the diagnosis of

MTLE. From a total of 121 possibly affected individuals, 98 were evaluated in this study (46 men, 52 women). A summary of clinical information from these patients can be accessed on the *Neurology* Web site (www.neurology.org). The number of affected individuals per family varied from 2 to 23 (mean 5), and most pedigrees showed segregation suggestive of autosomal dominant inheritance with incomplete penetrance (figure 1).

Clinical characteristics. Patients with clinical EEG criteria for MTLE. Sixty-eight individuals fulfilled the clinical EEG criteria for MTLE. Of these, 57 (84%) had simple partial seizures, which were more commonly characterized by epigastric sensation with other autonomic signs and symptoms, observed in 41 of 68 patients (60%). Fear sensation, accompanied or not by epigastric sensation and other autonomic signs and symptoms such as sudoresis, tachycardia, and piloerection, was experienced by 21 of 68 patients (31%). Other manifestations included complex hallucinations (misperception) in three patients, olfactory sensations in four, cephalic sensation in two, and nonlocalized ill-defined somato-sensitive symptoms in one. "Déjà vu" was mentioned by five patients only (7%). No auditory auras were reported, as this was an exclusion criterion. Complex partial seizures were present in 62 of 68 patients (91%). Automatism, generally oromandibular, occurred in 22 of 68 patients (32%), whereas dystonic posturing of hands was observed in only 5 patients (7%). Fifty-seven of 68 patients (84%) had rare secondary generalized tonic-clonic seizures. However, most of these occurred only in the beginning of the disease, with remission or improvement after treatment. History of earlier febrile seizure was positive in 4 of 68 patients (6%) with MTLE. Three of these patients had good seizure control on medication: one with simple febrile seizure and two with recurrent complex febrile seizure. Only one patient had refractory seizures and antecedent of complex febrile seizure. Spontaneous remission of partial seizures occurred in 15 of 68 patients (22%; mean age 37 years, ranging from 7 to 65 years). Good seizure control with medication was observed in 37 of 68 (54%; mean age 33 years, ranging from 8 to 66 years). Medically refractory seizures were found in 16 of 68 patients (24%; mean age 34 years, ranging from 20 to 43 years), 7 of whom underwent surgery. Detailed pathologic studies were not available owing to the surgical technique. The available fragments of mesial temporal tissue showed gliosis and neuronal loss, as usually observed in MTLE.

Affected individuals who did not fulfill criteria for MTLE. Eleven of 98 patients (11%) had recurrent afebrile seizures that could not be classified as partial seizures (mean age 40 years, ranging from 13 to 75 years). Five of these patients had seizures during sleep only, and all were described as generalized tonic-clonic seizures. All 11 patients had seizure remission and are off medication for at least 10 years (10 to 45 years).

Eleven of 98 patients (11%) had febrile seizures alone (mean age 18.5 years, ranging from 3 to 36 years). Age at the occurrence of febrile seizure ranged from 6 months to 6 years (mean 1.8 years). Febrile seizures were recurrent in five patients: three had simple febrile seizures and two had complex febrile seizures. Six patients had only a single episode of simple febrile seizures. Six of the 11 patients with febrile seizures alone belong to the same family (family P26; figure 1).

Eight of 98 patients (8%) had a single afebrile seizure (mean age 26 years, ranging from 12 to 42 years). In five patients, a partial onset was clearly identified, with clinical characteristics of complex partial seizures of temporal lobe origin in all but one. Four of the eight patients with a single afebrile seizure were from the same family (family P26; figure 1).

Classification of MTLE families according to clinical outcome. Benign MTLE only was seen in nine (41%) families (for additional information, please access www.neurology.org), with a total of 39 affected individuals. 27 of whom (70%) met the clinical criteria for MTLE. None of these patients with MTLE had history of febrile seizures, and six of them (22%) had seizure remission off medication at the time of evaluation. The remaining 21 patients with MTLE (78%) had good seizure control on medication.

Refractory MTLE only was seen in one small family (4%) (for additional information, please access www.neurology.org), with two affected sisters. Both of them have hippocampal atrophy and no history of febrile seizures. One of these patients underwent surgical treatment and is seizure-free after 1 year of follow-up.

Heterogeneous seizure outcome was seen in 12 families (52%) (for additional information, please access www.neurology.org), with a total of 57 affected individuals. Thirty-nine patients (68.5%) have MTLE. 9 patients had seizure remission, 16 patients have good seizure control on medication, and 14 patients have refractory seizures. Six of them underwent surgical treatment, and all but one are seizure-free after 5 months to 2 years of follow-up. The remaining patient continued to have auras and rare complex partial seizures. He had an incomplete anterior temporal resection and is waiting for reoperation.

EEG findings. Interictal EEG recordings were available in 64 patients. Seventeen individuals with remission or good seizure control did not attend the EEG appointments despite several attempts to contact them.

Epileptiform discharges were observed in 28 of 64 patients (43%): 6 in the right temporal region, 14 in the left temporal region, 7 in both temporal regions, and with a generalized distribution in 1 patient. Slow waves in the temporal regions were present in 10 of 64 patients (15%): 3 right temporal, 5 left temporal, and 2 bitemporal. EEG was normal in 26 of 64 patients (40%).

Seven patients with refractory seizures underwent ictal EEG recordings. Two patients had ictal EEG onsets in the right midinferomesial temporal region and two patients in the left midinferomesial temporal region. Two patients had bilateral temporal ictal EEG onsets. In the remaining patient, a single seizure was recorded on both temporal regions with right-sided predominance.

MR findings. We performed MR scans in 84 of 98 patients, including 44 patients with benign MTLE (13 with seizure remission and 31 with good seizure control), 16 patients with MTLE with refractory seizures, 10 patients with febrile seizures only, 10 patients with generalized tonic-clonic seizures only, 1 patient with a single generalized tonic-clonic seizure, and 3 patients with a single partial seizure. A summary of the MR findings for each subject is shown in the Web tables.

Hippocampal abnormalities were observed in 52 of 84 patients (62%): unilateral hippocampal atrophy with increased T2 signal in 41 of 84 patients (49%; 24 left and 17 right),

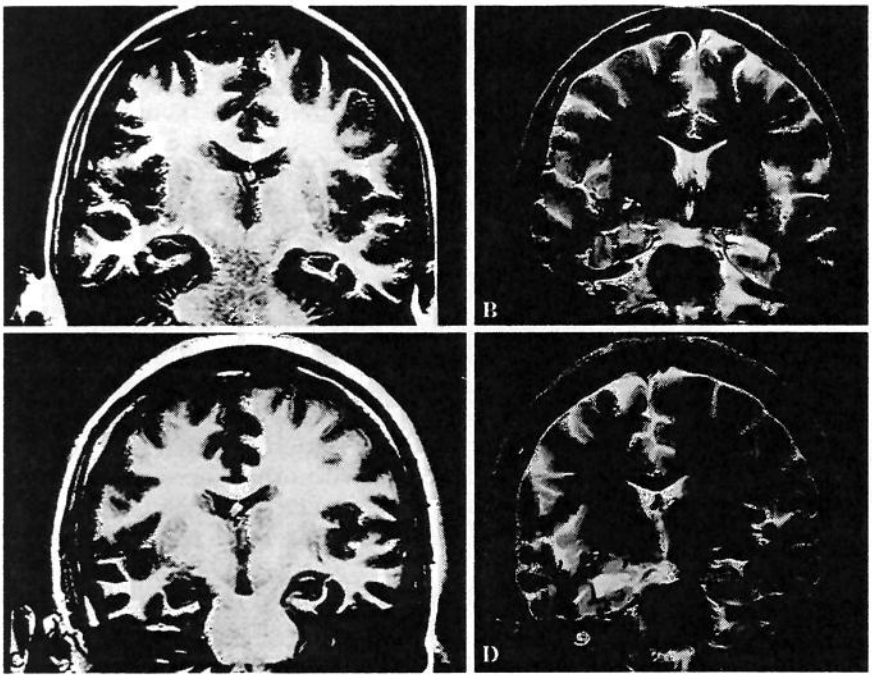

Figure 2. Illustrative images of hippocampal abnormalities in subjects with familial mesial temporal lobe epilepsy (MTLE). (A) Coronal T1 inversion recovery image shows left hippocampal atrophy and loss of internal structure in a 15-year-old girl with MTLE since 4 years old and rare partial seizures on carbamazepine monotherapy. The T2 fast spin echo images (not included here) showed hyperintense T2 signal. (B) Coronal T2 fast spin echo MR image from a 42-year-old woman who had a single complex partial seizure with secondary generalization at the age of 7 years shows left hippocampal atrophy with hyperintense signal. (C) T1 inversion recovery images show pronounced right hippocampal atrophy and loss of internal structures in a 33-year-old woman with MTLE since 2 years old. (D) The T2 fast spin echo images showed hyperintense T2 signal. Her seizures are controlled with carbamazepine monotherapy. See Patients and Methods for MR acquisition parameters.

bilateral hippocampal atrophy in 7 of 84 (8%), and abnormal hippocampal shape or axis in 4 of 84 patients (5%).

The distribution of hippocampal atrophy according to the seizure outcome groups was as follows: 6 of 13 patients (46%) with seizure remission, 16 of 31 (51%) of those with good seizure control under medication (figure 2), and all 16 patients with refractory MTLE had hippocampal atrophy by visual analysis. Hippocampal atrophy was found also in patients who did not fulfill the criteria for MTLE: 3 of 10 patients (30%) with febrile seizures alone, 6 of 10 patients (60%) with recurrent generalized tonic-clonic seizures, and 1 of 4 patients (25%) with a single partial seizure.

Altered shape of hippocampus without an abnormality of size or internal structure was identified in three patients: one patient with seizure remission, one who had a single partial seizure, and one who had a single simple febrile seizure. Abnormal axis of left hippocampus was observed in one patient with a single episode of simple febrile seizure (figure 3).

Additional abnormalities were seen in seven patients with MTLE with hippocampal atrophy: single or multiple small cystic lesions suggestive of neurocysticercosis in four, multiple lacunar infarcts in one, diffuse cerebral atrophy in one, and hydrocephalus with partial agenesis of corpus callosum in one patient. These additional abnormalities were not associated with poor seizure control, as two of them had seizure remission and three patients had good seizure control.

Additional abnormalities with hippocampal atrophy were also seen in patients with febrile seizure alone and generalized tonic-clonic seizures: one patient with febrile seizure alone had left hippocampal atrophy and multiple periventricular cysts, two patients with generalized tonic-clonic seizures had hippocampal atrophy and arachnoid cysts, and one had diffuse cerebral atrophy.

Other MR abnormalities with normal hippocampi are described in the tables on the Web version of this article.

MRI was normal in 24 of 84 patients (28%). This was found in 4 of 13 patients (31%) with benign MTLE with seizure remission, 12 of 31 patients (39%) with benign MTLE with good seizure control, 4 of 10 patients (40%) with generalized seizures only, 2 of 3 patients (66%) with a single partial seizure, and 2 of 10 of the febrile seizure group (20%).

Discussion. Over the last four decades, familial aggregation studies have shown evidence for an increased risk for epilepsy in relatives of probands with different types of epilepsy.[8,9] In addition, the presence of higher concordance rates for epilepsy in monozygotic than dizygotic twins provided two important pieces of evidence supporting the role of genetic factors in determining susceptibility to seizures.[10] However, partial epilepsies have been regarded as predominantly acquired disorders, and only recently have families segregating different forms of partial seizures been reported.[11-13] It is now generally accepted that susceptibility to different types of seizures probably reflects complex interactions of multiple factors, genetic and environmental, affecting neuronal excitability and that the most common genetic epilepsies display familial aggregation patterns that are not explained by segregation of a single autosomal gene.[8,14] However, some specific epilepsy syndromes, which aggregate in families, may result from definable monogenic abnormalities.

One of the major obstacles involved in the genetic study of epilepsy is the ascertainment and classification of affected subjects. As observed in our study, fam-

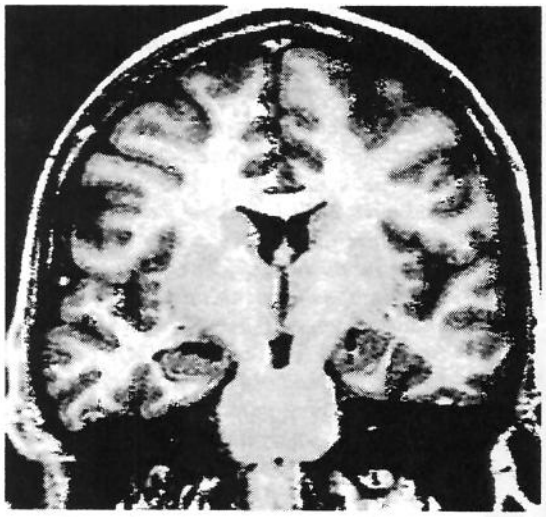

Figure 3. Coronal T1 inversion recovery image from a 31-year-old woman who had a single complex partial seizure with secondary generalization at age 7 years shows an abnormal axis of the left hippocampus.

ily history data are not always clearly obtained in the first interview, and there is a considerable number of underreported affected individuals, mainly among those who had seizures in early life or an isolated unprovoked or symptomatic episode such as a febrile convulsion. Therefore, careful clinical evaluation of affected and unaffected individuals as well as repeated interviews have proven to be very important for the acquisition of good family material for clinical and genetic studies, as well as the estimation of the frequency of familial cases. In addition, families with epilepsy may be constituted by clearly affected subjects and unaffected individuals that carry the susceptibility gene, which is illustrated by the evidence of incomplete penetrance in many of our pedigrees. Therefore, clinical and genetic studies must take possible diagnostic uncertainties into account.

Although understood as a disorder associated with febrile seizure and family history, TLE has been studied mostly in its classic presentation of medically refractory seizures, as it was the form observed in patients followed in epilepsy centers. Important to note is that many of the individuals evaluated here had no previous diagnosis of epilepsy, owing to a benign course or spontaneous remission throughout life. The frequency of positive family history among TLE patients in our clinic was ≈7%; however, we believe that this is an underestimation because, as discussed above, data about affected relatives are not always available. In addition, we have not included here patients with a family history whose possibly affected relatives could not be evaluated by one of us.

The first series describing familial TLE as a benign disorder was based on twin and nontwin families.[10] Unlike in other family studies of probands with refractory TLE, the affected individuals had a homogeneous pattern of TLE, with late onset and good outcome. MRI was normal, and EEG showed sparse temporal interictal epileptiform discharges in only 22% of subjects. A second report of familial TLE identified 36 affected individuals in 11 unrelated families with clinical heterogeneity.[12] Although the majority of these patients presented good seizure control, some of them had intractable epilepsy and required surgical treatment. MRI was available in 18 subjects and showed features of MTS in 11 (61%) of them.[12]

There are other forms of familial partial epilepsies in which affected subjects may present with clinical features of TLE. These include TLE with auditory auras,[15] in which clinical and EEG findings point to lateral temporal foci, and familial partial epilepsy with variable foci,[16] in which patients with TLE can be found among individuals with other forms of partial seizures. However, no evidence of MR abnormalities that could indicate MTS has been reported in these families.

It has been widely accepted, based on large series of surgical patients, that there is a strong correlation between MTS and severity of epilepsy. In addition, MTS identified by MRI has been associated with poor seizure control. However, our findings of MR abnormalities in patients with good outcome and seizure remission indicate that MTS is not found exclusively in medically refractory cases. Evidence for this has been already hinted at in the literature, including previous reports of sporadic patients with MTS.[17,18] However, follow-up of patients in these studies has been too short to provide any conclusions, different from our study, in which individuals with hippocampal atrophy have been seizure-free for over a decade. An MR study of families with febrile seizure has shown the occurrence of subtle hippocampal abnormalities even among asymptomatic individuals, suggesting a pre-existing damage leading to febrile seizure and/or MTLE.[19]

Detailed qualitative analysis of high-resolution MRI from our patients with familial MTLE showed abnormalities suggestive of MTS in 57% of these individuals, despite a heterogeneous clinical presentation. The hippocampal abnormalities ranged from abnormal shape or axis of the hippocampi to severe hippocampal atrophy with hyperintense T2 signal. Hippocampal atrophy was found in all patients with refractory seizures, but also in patients with good outcome, including those with seizure remission or a single seizure. This finding may indicate that hippocampal abnormalities are probably not the sole consequence of repeated seizures and that genetically determined mechanisms might play an important role in hippocampal damage, at least in these familial cases.

Despite the frequent finding of hippocampal abnormalities, history of febrile seizures among our patients was uncommon, similar to previous reports of familial TLE[10,20,21] and differently from most series of TLE patients.[21-25] This may suggest that the development of hippocampal pathology in familial MTLE is

not necessarily linked to prolonged febrile episodes early in life.

In our search for familial cases of MTLE, we have also found families that were not included in the present study, with only one individual clearly classified as having MTLE, but with other family members having seizures that could not be diagnosed as MTLE. We acknowledge here that these excluded families may represent one end of the spectrum of the same syndrome of familial MTLE. Quantitative and qualitative MR studies in this group of patients, including asymptomatic subjects, may be helpful to better understand the "sporadic cases" and the occurrence of other seizure manifestations among relatives of patients with MTLE.

This is the first time that MR evidence of MTS is reported in a large nonsurgical familial series. This is likely to be an important contribution for the understanding of the biology of MTS and its relationship to MTLE. Our findings of clear-cut MR evidence of MTS in adult individuals who had a single seizure or remission of MTLE after a few seizures indicate that MTS may be the cause, and not the consequence, of repeated seizures through life. In addition, we found a spectrum of hippocampal abnormalities, including atrophy, hyperintense T2 signal, and other subtle abnormalities, in children who had few seizures or only a single episode of febrile seizure. This suggests that these children, who belong to familial aggregates of MTLE, may be in the "silent period" of the natural history of MTLE and that underlying genetic mechanisms may lead them to develop the characteristic pathology of MTS very early in life, with different degrees of expression. Some may present with hippocampal abnormalities that could develop into MTS when exposed to environmental injuries, even before the onset of recurrent seizures. However, we acknowledge that repeated seizures through life probably cause further neuronal damage as indicated by several lines of evidence.[4,21,26-30]

We have shown that familial MTLE is clinically heterogeneous, although most affected individuals have a benign course of the disease. It is very likely that the different types of seizures occurring in the same family may have resulted from interactions of genetic or environmental modifiers or both. In addition, we found evidence of a strong genetic predisposition for the development of MTS, a lesion that was previously thought to be a predominantly acquired abnormality.

Acknowledgment

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Artigo 3

Hippocampal atrophy and T2 weighted signal changes in familial mesial temporal lobe epilepsy

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Hippocampal atrophy and T2-weighted signal changes in familial mesial temporal lobe epilepsy

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Abstract—*Objective*: To correlate the clinical phenotype with hippocampal volumes (HcVs) and signal changes in patients with familial mesial temporal lobe epilepsy (FMTLE). *Methods*: FMTLE was defined when at least two first-degree relatives in a family had a clinical-EEG diagnosis of MTLE. Hippocampal formation measurements were performed using 1- to 3-mm coronal T1-weighted MRIs. The presence of hyperintense T2 signal was evaluated by visual analysis. For statistical analyses, analysis of variance, χ^2 test, and regression analysis were used. *Results*: A total of 142 patients from 45 unrelated families were studied: 113 individuals with MTLE (80 with good seizure control) and 29 family members with other seizure types. There were 99 patients (69.7%) with hippocampal atrophy (HA). Sixty-seven of the 99 patients with HA also had a hyperintense T2 signal. Hyperintense T2 signal was associated with more severe HA ($p = 0.04$). Patients with refractory FMTLE had more frequent HA ($p = 0.03$) and hyperintense T2 signal ($p = 0.004$) and more severe atrophy ($p < 0.0001$). Duration of epilepsy correlated with HcV asymmetry index ($r^2 = 0.12$, $p = 0.00008$) and with the more atrophic hippocampi but not with contralateral hippocampi. *Conclusion*: In familial mesial temporal lobe epilepsy, seizure severity is variable in affected individuals. Hippocampal atrophy was present in 70% of these patients and 69% of these had an associated hyperintense T2 signal. Although hippocampal atrophy associated with abnormal T2 signal was more frequent and more severe in patients with poor seizure control, it was also frequent in affected individuals across families. These observations suggest that one or more genes resulting in familial mesial temporal lobe epilepsy predisposes both to the clinical features of mesial temporal lobe epilepsy and to the development of hippocampal sclerosis.

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Mesial temporal lobe epilepsy (MTLE) is frequently associated with mesial temporal sclerosis (MTS). MTS can be observed on MRI studies as hippocampal atrophy (HA), usually with abnormal signal intensity and other features such as loss of internal structure, abnormal shape and axis of hippocampus, and associated abnormalities in other mesial temporal structures. Although most patients with MTLE present with refractory seizures, they often have a good postoperative outcome, mainly when unilateral HA is identified on MRI scan.[1-4]

Familial mesial temporal lobe epilepsy (FMTLE) is a newly characterized syndrome, with different degrees of seizure severity, although the majority of patients have good seizure control.[5-7] In our previous study, we observed a high frequency of HA by visual MRI analysis, including individuals with seizure remission.[5] These findings suggest that the development of hippocampal abnormalities in these families may be related to genetic factors. Moreover, the identification of HA in patients with FMTLE with benign clinical course suggests that the presence of HA is not always associated with refractory epilepsy. The final phenotype is most likely dependent on the interaction with other modifying factors.

The use of hippocampal volumetric measurements allows quantification of the severity of HA, detection of subtle abnormalities, and the identification of bilateral atrophy. These objective data allow the comparison of different HA patterns among subgroups of patients. The increased sensitivity in identification of HA by volumetry has brought about clear advances in the characterization of MTLE.[8-14]

The objectives of this study were to perform hippocampal volumetry and evaluation of hyperintense T2 signal in a large group of patients with FMTLE and to correlate the MRI findings with clinical data.

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Patients and methods. *Ascertainment of subjects.* We included patients with FMTLE from three epilepsy centers: UNICAMP (Brazil), Montreal Neurologic Institute (Canada), and Austin and Repatriation Medical Center (Australia). All families were previously assessed for clinical and genetic studies, and all participating individuals gave informed consent, approved by the Ethics Committee of each center.

The diagnosis of MTLE was based on clinical and EEG findings.[15,16] Clinical criteria were history of simple partial or complex partial seizures (CPSs), or both, with characteristics of mesial temporal lobe origin, and no suggestion of any other partial epilepsy syndrome. Seizure semiology features that were consistent with mesial temporal origin were rising epigastric sensation, unexpected fear, and other psychic phenomena such as déjà vu and jamais vu, and CPS with staring, oroalimentary automatisms, dystonic posturing of one hand, and postictal confusion. Clinical description was obtained from each patient and one close relative who had witnessed at least one episode.

EEG criteria included presence of interictal epileptiform discharges over midinferomesial temporal regions or consistent intermittent slow wave abnormalities localized over the temporal areas, and no clear-cut epileptiform abnormalities elsewhere. Normal interictal EEGs did not exclude the diagnosis of MTLE. Nineteen patients had their seizures recorded and all had midinferomesial temporal lobe seizure onset.

Any suggestion of seizure onset outside the mesial temporal lobe by seizure semiology and EEG findings was an exclusion criterion. These included auditory or visual auras and interictal or ictal EEG epileptiform abnormalities over posterior temporal regions. When the semiology was not clearly defined, especially in patients who had only generalized tonic-clonic seizures (GTCSs) during sleep, these patients were not classified as having MTLE and were included in the "other seizure types" subgroup. History of risk factors, such as febrile seizures (FSs), head trauma, or meningitis was carefully investigated.

FMTLE was defined when two or more individuals in a family, first-degree relatives, presented with the clinical-EEG diagnosis of MTLE. MTLE patients who had a positive family history but whose relatives were not available for appropriate evaluation were not included in this study. Family members who had seizures, but who did not fulfill the criteria for MTLE, were also studied whenever possible, as long as they belonged to a family with two other individuals with defined MTLE. All affected subjects were asked to participate in an MRI study protocol.

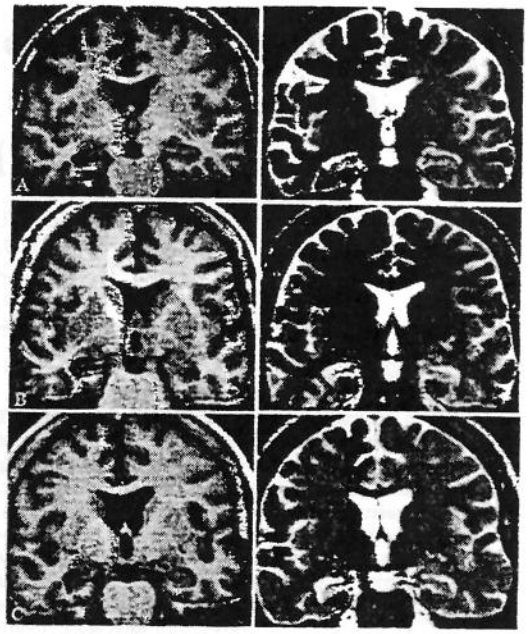
All patients had received appropriate clinical treatment with antiepileptic drugs, except for some individuals with very benign epilepsy seen on field trips who had never been treated, including some in whom the diagnosis of seizures was made only after our evaluation.

Clinical classification. Patients who fulfilled the clinical criteria for MTLE were divided into two groups, according to seizure outcome.[3] The first group included patients with benign MTLE with remission (seizure free for at least 2 years, off medication) or with good seizure control (patients on medication, with only rare CPSs [three/year]; patients who had up to two GTCSs/year, clearly related to abrupt withdrawal of antiepileptic drugs, but who had complete seizure control on medication, were also considered as "with good seizure control." The second group included patients with refractory MTLE (poor seizure control with appropriate anticonvulsant therapy) and who did not fit the criteria for category 1.

Patients with seizures, but who did not fulfill the criteria for MTLE were included in a third subgroup: patients with other seizure types: FSs only, single partial seizure (SPS), and a few GTCSs with no partial onset identified by history or unwitnessed (including those with single or recurrent episodes, all seizure free for at least 10 years).

MRI studies. All MRI scans were obtained in a 1.5-T Philips ACSIII (Philips Medical Systems, Best, the Netherlands), 1.5-T Siemens Magneton (Munich/Erlangen, Germany), or 2-T Elscint Prestige (Elscint, Haifa, Israel) scanner. We acquired T1- and T2-weighted MRIs in three orthogonal planes, as well as thin coronal (1- to 3-mm) T1 inversion recovery (IR) or gradient echo images, perpendicular to the long axis of the hippocampus, to optimize the evaluation of mesial temporal structures.

Hippocampal formation measurements were performed according to a standardized protocol.[8] We used 3-mm T1 IR images or 1-



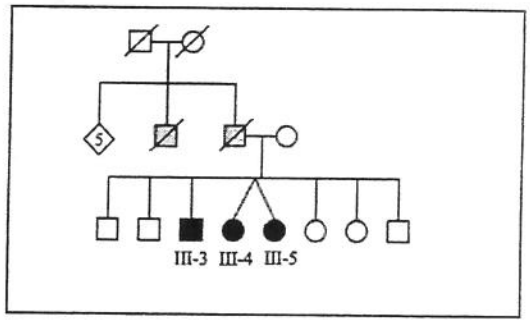


Figure 1. Coronal T1 inversion recovery and T2-weighted images from three siblings (III-4 and III-5 being dizygotic twins) with familial mesial temporal lobe epilepsy, from the family represented in the pedigree below the images. Hippocampal atrophy with hyperintense T2 signal and abnormal hippocampal internal structure are clearly identified in these three individuals. (A) Patient III-3 is a 50-year-old man who had had complex partial seizures (CPSs) with rare secondary generalization since age 4 years and has been off medication for several years. He has sporadic partial seizures only when he drinks alcohol. (B) Patient III-4 is a 47-year-old woman who had a simple febrile seizure when she was 2 years old and started having CPSs with occasional secondary generalization at age 9 years. She has frequent seizures, refractory to medication. (C) Patient III-5 is a 47-year-old woman who has had few seizures in life. Her first CPS with secondary generalization was at age 8 years. She never took antiepileptic drugs. Her sporadic seizures are associated with major stress or alcohol intake. Open squares and circles = unaffected; solid squares and circles = affected; circles and squares with slash = deceased.

to 1.5-mm three-dimensional T1 gradient echo images in the coronal plane for manual contouring following anatomic guidelines. The final hippocampal volume (HcV) was corrected by the variation in the total brain volume, to determine the presence of unilateral HA and symmetric or asymmetric bilateral HA. The ratio determined by the smaller and larger hippocampal volumes assessed the asymmetry index (HcAI) for each patient.

Control groups of healthy adult volunteers from two centers (n = 30 at Montreal Neurological Institute and n = 30 at UNICAMP) were used in the correction and determination of the final HcV for the respective patient populations. Because a difference in imaging acquisition parameters is reflected in different absolute volumes, we transformed all the volumetric data into Z-scores (number of standard deviations from the mean of each appropriate control group). HcVs or HcAIs 2 SD below the mean of the control groups were considered abnormal.

We also analyzed independently the presence of increased T2 hippocampal signal by detailed visual analysis of thin coronal T2-weighted spin echo or fast spin echo images.

Descriptive analysis. We described the corrected HcV and the HcAI from each patient, divided into clinical subgroups, and the inter- and intrafamilial variation.

Statistical analysis. Analyses of variance (ANOVA) was performed with post hoc pairwise comparisons, using the Tukey test, to determine differences in HcV among different subgroups, according to the clinical phenotypes described here. χ^2 tests were used to assess differences in frequency distribution of HA, hyperintense T2 signal, and history of risk factors. Present age, age at seizure onset, and epilepsy duration were correlated with HcV and HcAI. We also correlated the presence of abnormal T2 signal with HcVs.

Results. We performed high-resolution MRI scans in 142 patients with FMTLE who were members of 45 unrelated families. There were nine families ascertained at the Montreal Neurologic Institute, four at the Austin and Repatriation Medical Center in Melbourne, and 32 at UNICAMP, Brazil. Forty families had at least two individuals scanned (mean = 3, maximum = 20). All families with more than five evaluated patients were from Brazil. Two families had at least two individuals with MRI scans but only one of them had appropriate acquisition for volumetry.

There were 113 patients with a diagnosis of MTLE: 33 with refractory seizures and 80 with good seizure control (33 with seizure remission). Age at onset of habitual seizures varied from 1 to 56 years (mean = 10 years). History of earlier FS was identified in 13 (11.5%) of these patients with FMTLE, occurring in six of 33 patients (18.2%) with refractory disease and seven of 80 patients (8.8%) with a benign clinical course. None of our patients had had meningitis or head trauma prior to onset of epilepsy.

In addition, we studied 29 family members with other seizure types: 12 with FS only, four with SPSs, and 13 with GTCSs. Twelve of the 13 individuals who had GTCSs were seizure free for at least 10 years, off medication (one patient with GTCSs during sleep is seizure free for 2 years now, on medication).

HA was identified by volume measurement in 99 of 142 patients (70%): 48 unilateral (20 right and 28 left) and 51 bilateral (22 asymmetrical, with AI < 2 SD from mean of control group). Careful visual analysis of hyperintense T2 signal was possible in 97 of these individuals with HA and showed abnormal hyperintense signal in 67 of 97 patients (69%) (figures 1 and 2). HcV Z-scores of atrophic hippocampi showing increased T2 signal (from −8.47 to −1.55, mean = −4.38) were lower than those of atrophic hippocampi without T2 signal abnormalities (from −6.82 to −0.63, mean = −2.9) (ANOVA, F = 1.957, p = 0.00002, figure 3).

Hyperintense T2 signal was more frequently observed in patients with refractory seizures (Pearson $\chi^2[1] = 4.87$, $p = 0.027$, Fisher $p = 0.03$, Cohen kappa = 0.16). Patients with hyperintense T2 signal had older age at evaluation and longer epilepsy duration, as compared with patients with normal hippocampal T2 signal, but these differences were not significant. No differences were found regarding age at seizure onset in patients with and patients without abnormal T2 signal. In addition, patients with increased hippocampal T2 signal had smaller ipsilateral HcVs compared with those without hyperintense T2 signal (p = 0.041) (for this analysis we included volumes of smaller hippocampus of each individual).

HA was more frequent in the subgroup of patients with refractory FMTLE (29/33; 88%), as compared with patients with FMTLE with good seizure control (52/80; 65%) and patients with other seizure types (18/29; 62%) ($\chi^2[2] = 6.8$, $p = 0.03$).

Patients with refractory seizures had smaller hippocampi compared with patients with other seizure types (for this analysis we used the Z-score value of the smaller hippocampus for each subject): ANOVA, F = 4.8, p = 0.009. The Tukey test showed that patients with benign FMTLE had smaller hippocampi than patients with other seizure types and larger hippocampi than pa-

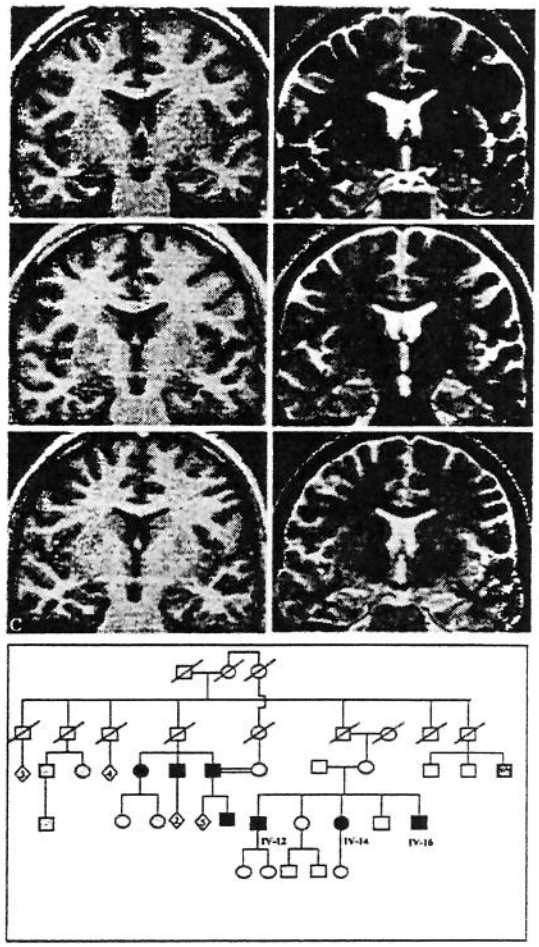


Figure 2. Coronal T1 inversion recovery and T2-weighted images of three siblings from one family with nine other affected and possibly affected individuals, showing unilateral hippocampal atrophy with hyperintense T2 signal and abnormal internal structure. (A) Patient IV-12 is a 37-year-old man who had onset of complex partial seizures at 2 years of age and has been seizure free and off medication since age 10 years. (B) Patient IV-14 is a 31-year-old woman who has had complex partial seizures since age 14 years, refractory to adequate antiepileptic medication. (C) Patient IV-16 is a 28-year-old man who has had well-controlled seizures since age 2 years. Open squares and circles = unaffected; solid squares and circles = affected; circles and squares with slash = deceased.

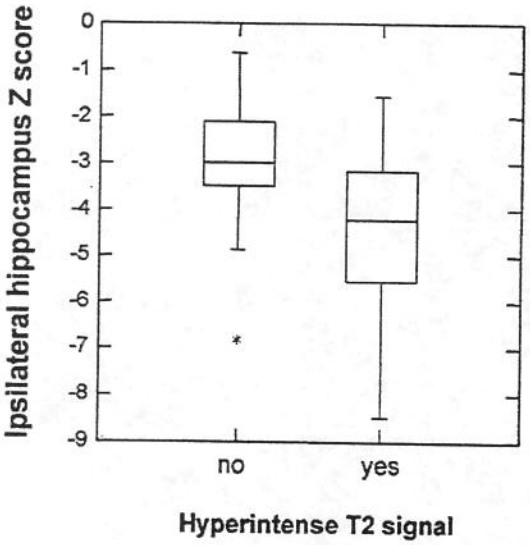


*Figure 3. Box and whiskers plot showing that patients with hyperintense T2 signal had smaller ipsilateral hippocampi, compared with patients with no hippocampal signal abnormalities. The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest. *Identifies an outlier. p = 0.00002.*

tients with refractory seizures, but these differences were not significant (p values = 0.98 and 0.09).

HcV AI was different among the subgroups of patients (ANOVA, $p < 0.0001$, figure 4). The pairwise comparisons showed that patients with refractory FMTLE had a more pronounced degree of atrophy when compared with those with benign MTLE and with patients with other seizure types ($p < 0.0001$). In addition, there was a difference between patients with benign MTLE and those with other seizure types ($p = 0.007$).

There was no difference in patient age at MRI scanning among the three groups (ANOVA, $F(2) = 2.5$, $p = 0.08$). Seizures started earlier in patients with refractory MTLE (mean age at seizure onset = 6.6 years), as compared with patients with benign FMTLE (mean age at seizure onset = 12.9) (ANOVA, $F(1) = 5.5$, $p = 0.02$). Consequently, patients with refractory seizures had longer epilepsy duration as compared with the other groups (ANOVA, $F(2) = 7.5$, $p = 0.0008$).

There was a correlation between HcAI and duration of epilepsy ($r^2 = 0.12$, $p = 0.00008$), although the value of r^2 indicates that only 12% of atrophy could be influenced by duration of epilepsy. Regression analyses showed that epilepsy duration was associated with patient's smaller hippocampi ($r^2 = 0.10$, $p = 0.0004$) but not with patient's larger hippocampi ($p = 0.39$).

History of FS among all patients with FMTLE was 11.5%. FSs were more frequent in those with refractory seizures (18%), as compared with patients with good seizure control (8%), but this was not significant. There was also a higher frequency of FS in patients with HA (12/99; 12%) as compared with those without HA (1/43; 2.3%), but the difference was also not significant. It was not possible to ascertain the exact number of individuals with complex FSs in this series; however, the majority of the individuals with history of FS had simple FS.

Analyses of intra- and interfamilial frequency of hippocampal atrophy and refractory seizures. Intra- and interfamilial frequency of HA was assessed in families with at least three affected individuals with MRI. There were 20 families that could be evaluated for this issue and the mean percentage of HA among family members was 77.5% (ranging from 33.3 to 100%). Twelve of these families had >75% of individuals with HA. The overall proportion of HA was similar across families despite the fact that 12 of 45 families (26.6%) had only individuals with good outcome. The proportion of individuals with refractory seizures was small across families without any indication for interfamilial heterogeneity.

Discussion. Although hippocampal abnormalities may not necessarily be associated with refractory seizures, no studies have been able to clarify this question so far. Most series report the identification of HA in surgical candidates. The difficulty in performing MRI investigations in large series of isolated patients with well-controlled MTLE may lead to underestimation of HA in patients with benign MTLE. Therefore, whether repeated seizures are the cause or the consequence of HA remains unanswered.

Among the 45 families, we found hippocampal abnormalities in many individuals who met the clinical-EEG criteria for MTLE but who had a benign clinical course. A history of FS was not frequently obtained (11.5%) in these patients with FMTLE. Although a history of FS was greater in the group of patients with refractory disease, it was not strongly associated with HA, as the majority of patients with HA had no identifiable risk factors. This supports the concept that simple FSs are a marker of increased seizure susceptibility rather than a cause of MTLE and HA.[17]

In this series, we identified HA by MRI volumetric measurements in 99 of 142 patients (70%). Although this study concentrates on volumetric measurements in order to facilitate statistical analysis and presentation of results, it is worth mentioning that 69% of our patients with HA also had hyperintense T2 signal and additional MRI evidence of hippocampal sclerosis, such as abnormal shape and internal structure of the hippocampal formation and other mesial temporal lobe structures. Their MRI findings cannot be distinguished from those observed in isolated patients with MTLE with hippocampal sclerosis, as can be observed in the figures presented. HA and hyperintense T2 signal were found in all subgroups of patients with FMTLE but were more frequent and more severe in the group of 33 patients with refractory seizures. Seizure onset occurred earlier in the group of patients with poor seizure control, and consequently epilepsy duration was longer in this subgroup of patients. The proportion of refractory FMTLE among all patients with HA was 29%. Thus 71% of patients with FMTLE with HA had a benign clinical presentation, including patients who had a single episode or seizure remission. This is much more frequent than reported in the literature,[18-20] with 11 to 42% of patients with MRI evidence of MTS being nonrefractory. However, most MRI studies of patients with TLE are biased to candidates for surgical treatment. Further large studies including patients with benign TLE will help to define if this high frequency of HA is also a feature of isolated TLE or if it is characteristic of FMTLE.

Another interesting point is the relatively high

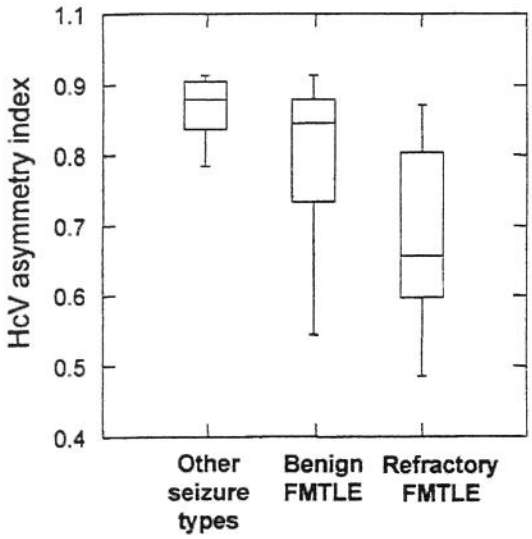


Figure 4. Box and whiskers plot showing difference in hippocampal volume (HcV) asymmetry index among patients with benign familial mesial temporal lobe epilepsy (FMTLE), refractory FMTLE and family members with other seizure types. Significant difference is indicated ($p < 0.0001$).

frequency of bilateral symmetric HA in our group of patients. Bilateral hippocampal abnormalities are a common finding in autopsy series of patients with TLE,[1] although in surgical series of patients with TLE, most have asymmetric hippocampal pathology.[8-13] Frequent bilateral symmetric HA in our families may be a further indication for a genetic background in the development of hippocampal abnormalities.

Our results support the hypothesis that imaging evidence of hippocampal sclerosis is not necessarily associated with poor seizure control. In addition, our study indicates that the hippocampal abnormality may be genetically determined in these families. Further support for this conclusion comes from the finding of asymptomatic HA. We have evaluated 36 asymptomatic first-degree relatives of patients with FMTLE.[21] Volumetric MRI studies demonstrated HA and other signs of MTS, including hyperintense T2 signal, in 34% of these asymptomatic family members.[21]

Familial TLE is likely to be genetically heterogeneous and the association with hippocampal pathology may vary among families. Moreover, there is a possibility that inherited HA and other MRI signs of MTS are not related only to the classic syndrome of MTLE. A possible interaction of other genetic, as well as environmental factors, may determine different phenotypes in patients with hippocampal abnormalities.

Acknowledgment

The authors thank all the patients and their families.

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Artigo 4

MRI evidence of hippocampal sclerosis in asymptomatic first-degree relatives of patients with familial mesial temporal lobe epilepsy

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Arch Neurol *2002 Dec 59:1891-1894*

Magnetic Resonance Imaging Evidence of Hippocampal Sclerosis in Asymptomatic, First-Degree Relatives of Patients With Familial Mesial Temporal Lobe Epilepsy

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Objective: To investigate the presence of hippocampal atrophy (HA) and other magnetic resonance imaging (MRI) signs of hippocampal sclerosis (HS) in asymptomatic relatives of patients with familial mesial temporal lobe epilepsy (FMTLE).

Methods: We invited first-degree, asymptomatic relatives of patients with FMTLE to participate in our MRI protocol. After obtaining informed consent, all participating individuals underwent an MRI examination. Hippocampal abnormality was determined by qualitative and volumetric analyses, using a standard protocol.

Results: We studied 52 asymptomatic individuals (27 men), with a mean age of 32 years (range, 7-71 years), from 11 families with FMTLE. Volumetric studies showed HA in 18 (34%) of 52 individuals: 11 had left HA and 7 had bilateral HA. In addition, careful visual analysis of T1- and T2-weighted images showed additional classic MRI signs of HS (such as abnormal T2 signal and/or abnormal internal structure) in 14 of these 18 individuals. There was no age difference between individuals with and without HA (*t* test, $P=.80$).

Conclusions: Our findings indicate that MRI evidence of HS is not necessarily related to seizure severity and may occur in individuals who never had seizures. In addition, these observations strongly indicate that HS in FMTLE is not a consequence of recurrent seizures and is determined by a strong genetic predisposition. The determination of seizure severity in patients with FMTLE probably depends on the interaction of different factors, both genetic and environmental.

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FAMILIAL MESIAL temporal lobe epilepsy (FMTLE) is a well-characterized syndrome that occurs in a large proportion of affected individuals with magnetic resonance imaging (MRI) evidence of hippocampal sclerosis (HS), including quantitative analyses.[1-3] The identification of clear-cut hippocampal atrophy (HA) and additional MRI signs of HS in patients with a benign clinical course in these families supports the theory that a genetic factor determines hippocampal pathologic abnormalities in FMTLE.[1,3] In addition, the finding of subtle hippocampal malformation in asymptomatic relatives of patients who present with complex febrile seizures[4] suggests that inherited dysgenetic abnormalities may lead to a predisposition to seizures in these families. The MRI findings for family members asymptomatic for FMTLE have not been previously reported. The investigation of mesial temporal abnormalities in high-resolution MRI in first-degree relatives of familial patients can be helpful for investigating if these families segregate MRI evidence of HS in individuals without clinical manifestation of the disease. The objective of this study was to investigate whether asymptomatic relatives of patients with FMTLE have MRI evidence of HS.

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METHODS

Familial mesial temporal lobe epilepsy was defined as 2 or more family members diagnosed as having mesial temporal lobe epilepsy by clinical and electroencephalographic (EEG) criteria.[1] The MRI findings of affected individuals with FMTLE were reported previously.[1] We invited all asymptomatic, first-degree relatives of these affected individuals to participate in the present study and to undergo an MRI examination. All individuals signed a written consent form, approved by the ethics committee of our institution. All individuals ascertained for this study were questioned about history of febrile or afebrile seizures. Parents and older relatives were also interviewed to corroborate the clinical information.

The MRIs were performed in a 2T scanner (Prestige; Elscint Ltd, Haifa, Israel), with

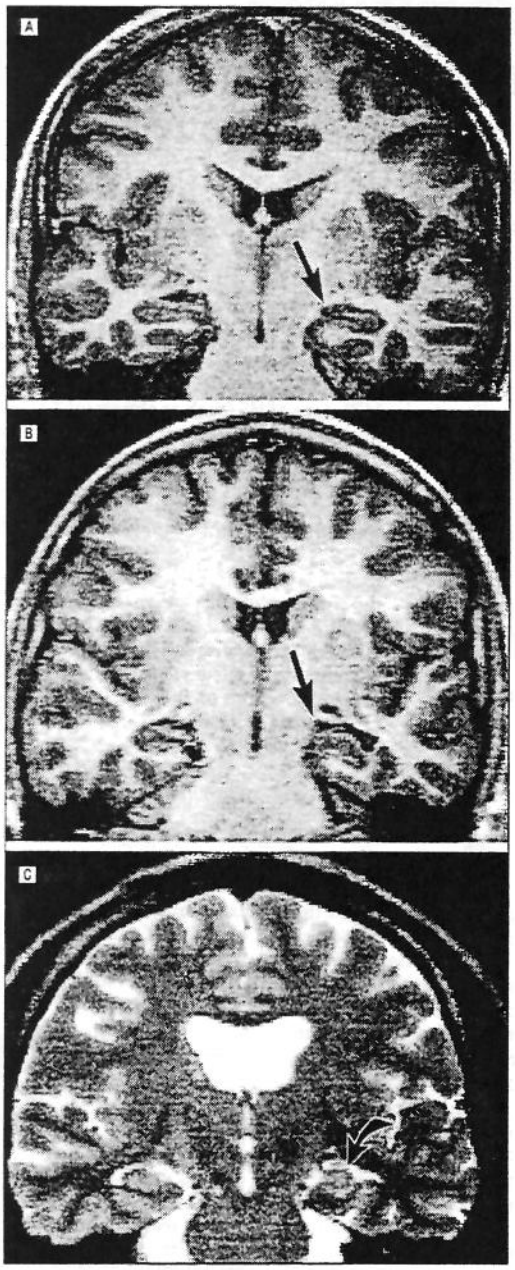

Figure 1. Hippocampal abnormalities in 3 asymptomatic individuals from families with mesial temporal lobe epilepsy. A, Coronal T1 inversion recovery image of a 14-year-old, asymptomatic boy (patient 11 in the Table) shows flattened and atrophic left hippocampus (arrow). B, Coronal T1 inversion recovery image from patient 5 in the Table. The left hippocampus is atrophic and bent clockwise and has an abnormal "irregular" shape (arrow). C, Coronal T2 fast spin echo image from patient 15 in the Table. The left atrophic hippocampus has an abnormal "rounded" shape (arrow). In addition, the fusiform gyrus and collateral sulcus on the left have an abnormal shape. Note also the absence of septum pellucidum.

T1 and T2 acquisitions in 3 orthogonal planes. The MRI acquisition variables were as follows: (1) sagittal T1 spin echo; 6 mm thick; flip angle, 180°; repetition time (TR), 430; echo time (TE), 12; matrix, 200×350; and field of view (FOV), 25×25 cm; (2) coronal images, perpendicular to long axis of hippocampus, defined on the sagittal images: (a) T2-weighted and proton density fast spin echo; 3 mm thick; flip angle, 160°; TR, 4800; TE, 108/18; matrix, 256×256; FOV, 22×22 cm; (b) T1-weighted inversion recovery; 3 mm thick; flip angle, 200°; TR, 2800; TE, 14; inversion time, 840; matrix, 130×256; and FOV, 16×18 cm; (3) axial images parallel to the long axis of the hippocampi: (a) T1-weighted gradient echo; 3 mm thick; flip angle, 70°; TR, 200; TE, 5; matrix, 180×232; and FOV, 22×22 cm; (b) T2-weighted fast spin echo; 4 mm thick; flip angle, 120°; TR, 6800; TE, 129; matrix, 252×328; and FOV, 21×23 cm; and (4) T1-weighted 3-dimensional gradient echo with 1-mm isotropic voxel, acquired in the sagittal plane for multiplanar reconstruction (1 mm thick; flip angle, 35°; TR, 22; TE, 9; matrix, 256×220; and FOV, 23×25 cm).

Hippocampal formations and total intracranial volumes were manually delineated on coronal inversion recovery images using software developed by the National Institutes of Health (NIH-Image, National Institutes of Health, Bethesda, Md), and anatomic guidelines were obtained from a standard protocol.[5] For determination of normal variables, hippocampal volumes were obtained in a group of 30 healthy volunteers (20 women; mean age, 32 years; range, 18-62 years). We calculated the absolute volumes for each hippocampus, corrected for variation of total brain volume to evaluate unilateral and bilateral volume loss.[5] We also obtained an asymmetry index (AI) for each patient (defined as the ratio of the smaller by the larger hippocampus). Volumes and/or AIs that were 2 SDs below the mean values of control group were indicative of HA.

In addition to volumetric studies, we performed careful systematic visual analysis of all MRIs, including T1- and T2-weighted images, for identification of other MRI signs of HS in these individuals. Visual assessment of hippocampal integrity accounted for hippocampal signal, internal structure and shape of hippocampi, and other mesial temporal structures. Images were analyzed on a Silicon Graphics workstation (O2; Silicon Graphics Inc, Mountainview, Calif) with imaging postprocessing software (OmniPro2; Elscint Ltd) that allows changing windowing (contrast and brightness), realignment of images, and multiplanar reconstruction. We paid special attention to the format of hippocampi along its entire axis and the morphologic findings of the adjacent mesial temporal structures.

Hippocampal volumes and AIs from each subject were transformed into *z* scores (standardized scores that express the number of SDs away from the mean of the control group). The *z* scores below −2 (2 SDs below the mean of healthy controls) were indicative of HA. We used the 2-tailed *t* test to compare the distribution of ages at MRI scan between individuals with and without HA.

RESULTS

We evaluated 11 of 32 families with FMTLE, with a total of 52 subjects (27 men) (mean age, 32 years; range, 7-71 years; with no difference compared with the control group; analysis of variance; $P=.80$). We found HA (**Figure 1**) in 18 (34%) of the 52 individuals: 11 unilateral (all left) and 7 bilateral (**Table**).

There was no difference in age at MRI between individuals with and without HA (*t* test, $P=.80$). In addition to HA, we found additional signs of HS in the visual analysis of MRIs in all but 3 individuals (Table). In-

Summary of Data From the 18 Asymptomatic Family Members With Hippocampal Abnormalities*

Patient No./Relationship With MTLE Patient/ Age at Study, y	Side of HA	RHV z Score	LHV z Score	AI (z Score)	Increased T2 Signal	Loss of Internal Structure	Abnormal Shape and Axis
1/Sister/36	Left	−1.3	−2.0	0.93 (−0.05)	Right	No	R>L
2/Brother/33	Left	−0.5	−2.4	0.85 (−2.79)	Left	No	No
3/Sister/43	Left	1.8	−0.1	0.86 (−2.18)	No	No	No
4/Father/68	Bil	−2.0	−2.7	0.92 (−0.35)	Bil	Bil	Bil
5/Son/15	Left	−1.5	−2.2	0.93 (−0.12)	Left	Left	Left
6/Sister/48	Bil	−2.9	−3.6	0.91 (−0.55)	No	No	No
7/Sister/35	Left	−0.8	−2.7	0.84 (−2.96)	No	No	No
8/Son/25	L>R	−2.3	−3.5	0.87 (−2.08)	L>R	Bil	Bil and abnormal FG
9/Daughter/7	Left	0.9	−0.7	0.88 (−1.60)	Left	No	Left and abnormal FG
10/Daughter/15	Left	−0.3	−1.9	0.86 (−2.27)	Left	Left	Left
11/Brother/14	Left	−0.3	−2.8	0.80 (−4.39)	Left	Left	Left
12/Brother/18	Bil	−3.1	−3.6	0.93 (0.00)	Bil	Bil	Bil
13/Mother/43	Bil	−3.3	−3.5	0.95 (0.63)	Bil	Bil	Bil
14/Brother/10	Bil	−4.8	−4.9	0.96 (0.85)	Left	Bil	Bil and abnormal FG
15/Brother/26	Left	−0.5	−3.4	0.76 (−5.57)	Left	Left	Left and abnormal FG
16/Brother/40	Bil	−4.9	−5.2	0.93 (0.11)	No	No	Bil and abnormal FG
17/Brother/35	Left	−1.1	−2.1	0.90 (−0.92)	Left	No	Left and abnormal FG
18/Sister/27	Left	−1.4	−2.1	0.92 (−0.19)	Left	No	Left and abnormal FG

*MTLE indicates mesial temporal lobe epilepsy; HA, hippocampal atrophy; RHV, right hippocampal volume; LHV, left hippocampal volume; AI, asymmetry index; Bil, bilateral; L, left; R, right; and FG, fusiform gyrus. The *z* score is the number of SDs below the mean of the control group.

creased T2 signal and/or loss of internal hippocampal structure was found in 14 of the 18 individuals with HA. Abnormal shape and axis of the hippocampal formation were present in 8 individuals (Figure 1). Additional abnormal anatomy of the mesial temporal structures, including enlargement of the fusiform or parahippocampal gyri and the collateral sulcus, was identified in 7 of the 18 individuals (**Figure 2**).

COMMENT

Both HS and HA have been associated with refractory seizures and good postoperative outcome in unilateral mesial temporal lobe epilepsy.[6-8] The MRI evidence of HS includes HA and other abnormalities, such as abnormal signal intensity,[5] loss of internal structure, and abnormal shape and orientation of hippocampal formation. Hippocampal atrophy is a reliable MRI indicator of HS and easy to quantify, thus allowing a more objective analysis. Furthermore, several studies[9,10] reported a robust correlation between the degree of HA and histopathologic findings. The real frequency of HA in patients with good seizure control is not yet well established. However, in our series of patients with FMTLE, we observed HA by visual analyses in 57% of individuals studied, including patients with a single episode or seizure remission.[1] In a subsequent multicentric study, we found HA by volumetric study in 77% of affected individuals with FMTLE.[3] This indicates a strong genetic factor in the development of hippocampal pathologic findings in these patients with FMTLE.

The observation of HA by volumetric measurements in first-degree, asymptomatic relatives of patients with seizures in these families further corroborates our previous hypothesis and raises the question of the cause-and-effect relationship between HS and epilepsy. Our findings indicate that MRI evidence of HS is probably genetically determined in these families, and the occurrence and prognosis of seizures may depend on additional environmental factors and possibly modifying

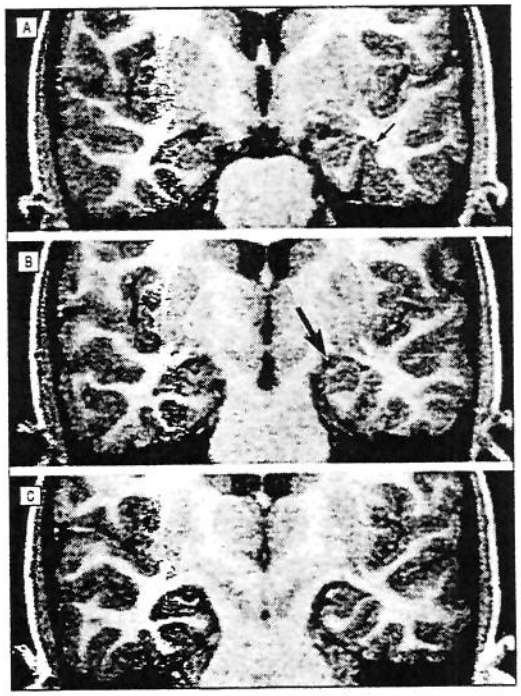

Figure 2. Mesial temporal abnormalities extending to the parahippocampal and fusiform gyri, as well as the collateral sulcus (small arrow) on the left (A) in a 7-year-old, asymptomatic girl with left hippocampal atrophy (arrow) (B) determined by magnetic resonance imaging volumetric measurements (C) (patient 9 in the Table).

genes. For example, morphologic abnormalities of hippocampal formation may represent mild phenotypes with susceptibility for developing full-blown HS in the presence of some types of injury. On the other end of the spectrum, there may be individual genetic effects strong enough to induce HS and temporal lobe epilepsy with minimal influence of environmental factors.

In addition, we found MRI signs suggestive of mesial temporal lobe dysgenesis in 8 of 18 individuals with HA. This may represent an inherited malformation of the mesial aspects of temporal regions that is not necessarily associated with seizures. The morphologic development of the entire hippocampal formation seems to follow a complex process of rotation and folding. The folding of dentate gyrus is especially marked in higher mammals.[11] In the mature hippocampus, the cornu ammonis and dentate gyrus form 2 U-shaped, interlocking laminae.[11] In normal circumstances, the internal structure of the hippocampus is the same in its different segments.[11] This pattern of internal structure is clearly altered in HS.[5,8-11] It is reasonable to assume that there might be a developmental basis of HS or some heralds of subsequent HS. This correlates with the finding of subtle hippocampal malformations described in asymptomatic siblings of patients with febrile seizures,[4] indicating a previous, genetically determined abnormality that in the presence of other modifying factors may be associated with different phenotypes.[12]

A recent report[13] provided pathologic confirmation of hippocampal malformation occurring without the presence of widespread cortical dysgenesis in an adult with temporal lobe epilepsy in whom MRI demonstrated bilateral hippocampal abnormalities. Postmortem examination revealed abnormal position and complex convolutional malformations isolated to the hippocampal formation, including verticalization of the hilus of the dentate gyrus and an excessively long and folded CA1.[13]

Seizures are clinical events triggered by abnormal firing of a large number of interconnected neurons. Subclinical EEG seizure discharges and interictal epileptiform discharges have a complex neurobiological substrate[14] and are a common finding in patients with epilepsy. On the other hand, the true incidence of EEG abnormalities in asymptomatic individuals is unknown. One may speculate that these asymptomatic individuals with MRI evidence of HS may in fact have interictal EEG abnormalities and even subclinical EEG seizures. However, given the random nature of these possible EEG abnormalities and the difficulties and cost involved in long-term EEG monitoring, these subclinical phenomena would be difficult to rule out. The absence of difference in age in individuals with HA compared with those who did not have abnormal hippocampi is another important indicator that this abnormality is probably the cause and not the consequence of ongoing ictal discharges. In conclusion, the MRI evidence of HS and hippocampal malformation in unaffected family members is indicative of preexisting predisposition to seizures in FMTLE that is modulated by other modifying factors. Our findings further support the hypothesis of a genetic inheritance of HS in these families with mesial temporal lobe epilepsy.

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All authors take equal responsibility for the design and data acquisition and interpretation of this study.

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Artigo 5

Outcome of surgical treatment in patients with familial mesial temporal lobe epilepsy

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Outcome of surgical treatment in patients with familial mesial temporal lobe epilepsy

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Word count: title (12), abstract (182), text (1848)

Figures: 2

Tables: 1

References: 14

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Abstract

Objective: To describe postoperative outcome in patients with familial mesial temporal lobe epilepsy (FMTLE).

Design/Methods: We studied FMTLE patients who underwent surgical treatment for refractory seizures. FMTLE was defined when at least two individuals in a family had clinical-EEG diagnosis of MTLE. Preoperative investigation included MRI, interictal/ictal EEGs and neuropsychological evaluation. We used Engel's classification for postoperative outcome.

Results: To date 20 FMTLE patients were operated, with one to nine years follow-up (mean 4.8 years). Hippocampal atrophy (HA) and other signs of mesial temporal sclerosis (MTS) were present in 18 patients (15 unilateral). Seizures were recorded in 19 patients. Seventeen patients (85%) are in class I. Two patients had normal hippocampal volumes (HcV): one (5%) is in class II and the other (5%) in class IV (she developed extra temporal seizures after surgery). One patient (5%) had bilateral HA and is in class III. Qualitative histopathology showed MTS with different degrees of severity.

Conclusion: Refractory FMTLE patients have good surgical outcome when unilateral or clearly asymmetrical HA is identified. Preoperative investigation should be the same as in patients with sporadic refractory MTLE.

Introduction

Mesial temporal lobe epilepsy (MTLE) is the most common form of partial epilepsy in adults and up to 50% of patients present with refractory seizures. Surgical treatment has an excellent prognosis, particularly when unilateral hippocampal atrophy (HA) on MRI and ipsilateral ictal and interictal EEG abnormalities are present [1-5].

The familial form of MTLE (FMTLE) has been recently established as a well-defined clinical syndrome, accounting for approximately 7% of patients with TLE [6-8]. Among the 22 families studied in our previous clinical-MRI report, there were up to 23 affected individuals per family (mean of 5). All possibly affected individuals underwent detailed clinical evaluation and EEG recordings whenever possible. Most families with MTLE have patients with different seizure severity; characteristically few patients have refractory seizures, and the majority of affected individuals have benign MTLE [6-8]. The presence of HA on MRI was observed in 57% of our series of 84 patients with FMTLE [6]. HA and other MRI signs of mesial temporal sclerosis (MTS) were present in patients with refractory seizures as well as in individuals with benign MTLE or a single seizure. In addition, we found MRI evidence of MTS in 34% of asymptomatic first-degree relatives of patients with FMTLE [9]. These observations suggest a strong genetic factor determining the development of HA. However, if we look only at patients with refractory FMTLE, they appear to have a clinical course similar to that of patients with sporadic MTLE who are candidates for surgical treatment [10-14].

Since a genetic form of epilepsy might be suspected to relate to a more diffuse or generalized process, the question was raised if surgical treatment should be considered in patients with FMTLE, even when they had intractable epilepsy. The objective of this study is to describe surgical outcome in a group of patients with refractory FMTLE and to assess if that differed from outcome in patients with sporadic MTLE.

Methods

FMTLE was defined when at least two individuals in a family had a clinical-EEG diagnosis of MTLE. We included patients from the University of Campinas (UNICAMP; Brazil) and the Montreal Neurological Institute (MNI; McGill University, Canada).

Patients underwent routine pre-operative investigation. All underwent serial routine interictal EEGs and prolonged video-EEG monitoring. All had a high-resolution MRI scan, including thin (1-3mm) coronal T1weighted images and T2 weighted coronal images, perpendicular to the long axis of the hippocampal formation [6,7].

The surgical technique consisted of anterior temporal lobe resection plus amygdalohippocampectomy (ATL) or selective amygdalohippocampectomy (SAH). Post-operative assessment was performed by clinical evaluation using Engel's classification of outcome scale [15]; in summary: I seizure-free, II rare seizures (less than 3/year), III improvement in seizure control (more than 90% reduction), IV no significant improvement.

After surgical excision, the tissue was fixed for 12 to 24 hours in 10% buffered formalin, then cut anteroposteriorly, embedded in paraffin and sectioned. Staining was carried out using Cajal's gold chloride sublimate, Luxol fast blue, and hematoxylin-eosin. Qualitative histopathology of surgical specimens was performed with particular attention to distribution of neuronal loss in different hippocampal subfields. We used the term MTS, to include neuronal loss and astrogliosis in the hippocampus, the adjacent entorhinal cortex, and the amygdala[14]. Based on a qualitative and descriptive hystopathological evaluation, we defined 3 categories: A) No definite neuronal loss or gliosis in mesial temporal structures; B) Mild degree of MTS; and C) MTS with marked neuronal loss and gliosis. We did not perform quantification of cell loss or sprouting.

Results

1. Clinical data:

Among the 32 unrelated MTLE families followed in both epilepsy centers we evaluated 162 affected individuals. Of these 31/162 individuals (19%) were considered to have refractory seizures. To date, 20 refractory FMTLE patients (10 men) from 17 unrelated families underwent surgical treatment (10 from MNI and 10 from UNICAMP). All these operated patients belonged to families that were properly evaluated and had at least two affected individuals (first-second degree relatives) with clinical-EEG criteria for MTLE (mean of 4.6 affected individuals/family and maximum of 23).

The mean follow-up after surgery is 4.8 years now (ranging from 12 months to 9.1 years). All retrievable data are shown in table 1.

Present age varied from 19 to 52 years (mean=37), and mean age at seizure onset was 5 years (3 months to 14 years). Febrile seizures during childhood occurred only in 6 (30%) patients. One patient had an antecedent of head trauma during childhood. Three (15%) patients (#s 8, 9 and 20 in table 1) had a history of status epilepticus.

2. Pre-operative investigation:

Eleven of 20 patients had bilateral epileptiform discharges in ictal and/or interictal EEGs. All patients underwent prolonged video-EEG monitoring. Seizures were recorded in all but one patient (#4). Ictal scalp EEGs showed exclusively unilateral antero-mesial temporal lobe seizure onset in 13/19 (68%) patients, and bilateral EEG seizure onset with clear lateralization to one side (always concordant with the side of HA) in 6/19 (32%). Four patients had depth electrode recordings (seizures recorded in two) and eletrocorticography was performed in 5 patients.

All but two patients had MRI findings of MTS on visual assessment: HA associated with hyperintense T2 signal, hypointense signal and loss of internal structures on T1-IR images and abnormal shape and axis of the hippocampus (figure 1). Volumetric

studies were performed in 15 patients and showed unilateral HA in 11 patients (73%), asymmetrical bilateral HA in 3 patients (15%) and confirmed normal hippocampal volumes (HcV) in the two patients with normal MRI on visual analysis. Only two patients did not have hyperintense T2 hippocampal signal (the only two patients with normal hippocampal volumes). Ipsilateral amygdalar atrophy with hyperintense T2 signal was also observed in 14 patients.

All operated patients had EEG abnormalities concordant with the side of the more atrophic hippocampus. One patient with unilateral HA was re-operated 12 months ago due to a limited mesial temporal resection and is now seizure-free.

Two patients from Brazil (#14 and 17 on table) had small cystic lesions in the temporal regions suggestive of neurocysticercosis (ipsilateral in one and contralateral in the other), associated with clear-cut HA and other signs of MTS, including hyperintense T2 signal. None of them show clinical or MRI improvement after previous treatment with albendazole.

3. Surgical treatment:

Surgical decision was based on all available data, similar to the approach in refractory MTLE patients with no family history. Surgical technique depended on the surgeon's experience and consisted of selective amygdalohippocampectomy (SAH) or anterior temporal lobe resection including the amygdala and hippocampus (ATL). Ten/20 patients were operated on the left and 10 on the right side. SAH was performed in 6/20 (30%) patients and ATL in 14/20 (70%).

4. Pathological findings:

Surgical specimens adequate for pathological studies were not available in six patients since the tissue was removed by aspiration. Pathological data were available in 14 patients and showed neuronal loss and gliosis typical of MTS, with predominant neuronal loss in CA1(figure 2), CA3 and dentate gyrus with sparing of CA2 in nine

patients. Although no quantitative analyses were performed, there were different degrees of cell loss, from mild to severe MTS (Table).

In one patient there was mild neuronal loss and gliosis in the amygdala/parahippocampus fragments (the fragments containing hippocampal tissue were not adequate for analysis of neuronal loss in the hippocampal subfields. In one patient there was neuronal loss and gliosis in amygdala and end folium sclerosis. No significant abnormalities were observed in the small fragments available for the pathologist in the remaining three patients, including one of the two patients with normal hippocampal volumes.

5. Postoperative outcome:

All patients have at least one year follow-up (mean of 4.8 years, up to 9.1 years follow-up). Seventeen (85%) of these patients are in Engel's class I (see table 1). The only patient in class II (patient #6) had normal HcV and histopathology, and was operated based on intracranial EEG recordings. The only patient in class III (patient #20) had bilateral asymmetrical HA and was operated in the more atrophic side (ipsilateral to seizure lateralization in ictal EEG). The only patient in class IV (patient #9) had normal MRI, bilateral asymmetrical interictal and ictal EEG abnormalities, and confirmed MTS on post-operative hystopathology. She developed another seizure pattern, compatible with perisylvian origin. She was a member of a family with FMTLE ascertained at the MNI but she was investigated and operated at another hospital.

The two Brazilian patients with neurocysticercosis associated to unilateral HA are seizure-free after 2.8 and 3.1 years respectively.

Discussion

Patients with refractory MTLE who have concordant clinical, EEG and MRI findings are expected to have an excellent postoperative outcome, with up to 94% of them becoming seizure-free when all these data are exclusively unilateral or clearly asymmetrical [5]. Although the etiology of the pathological findings of MTS is still not completely clarified, removal of the atrophic mesial temporal structures seems to be curative in these patients [10,12,14].

In FMTLE there are families with exclusively well controlled or remitted patients [8]; however, most families include some individuals with refractory seizures [6,7]. The observation of HA and hippocampal signal abnormalities on MRI in up to 57% of familial MTLE patients, including individuals with benign epilepsy and even those with seizure remission. Although we have strong evidence for the presence of a major gene determining susceptibility to seizures in families with MTLE, this issue will only be settled when this major gene is identified. To date, our data indicate that a genetic factor might be responsible for the development of hipocampal pathology [6] and that the severity of the epilepsy phenotype could be the result of modifying factors, genetic or environmental, that might interact to determine seizure outcome in each patient [6-9]. In addition, questions related to what specific genetic defects would cause MTS as the pathology in MTLE in some affected family members but not in others; and the relationship between seizure severity and hipocampal atrophy, will likely to be solved only when the molecular mechanisms underlying FMTLE are better understood.

Complex febrile seizures were identified in 3 patients (15%), all of them from the MNI. The frequency of patients with complex febrile seizures in the present series is higher when compared to that of overall FMTLE (6%) [6]. However, this figure is lower when compared to reported surgical series of TLE from the same institution (40%) [10].

Surgical results in our patients with refractory FMTLE associated to HA and hyperintense T2 signal are similar to those observed in sporadic patients. We observed an excellent surgical outcome (Engel's class I) in 17/20 (85%) patients and good results in another patient (Engel's class II), totaling 90% of patients with significant improvement.

This includes patients with bilateral asymmetrical hippocampal abnormalities identified by MRI, as we frequently encounter among sporadic refractory MTLE patients.

Despite the lack of pathological confirmation in all operated patients, the available pathology reports showed variable degrees of MTS and there was no difference in the pattern of histopathological abnormalities compared to that in sporadic MTLE patients.

The investigation of patients with FMTLE should not differ from that of patients with sporadic MTLE, and the surgical decision should be based on the same clinical-EEG-imaging evidence for seizure lateralization.

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Legends for table

Title: Table 1. Summary of clinical data

CFS: complex febrile seizures; * 9hs duration with meningitis

** patients who underwent intracranial EEG investigation

SPS: simple partial seizures; CPS: complex partial seizures; GTCS: generalized tonic-clonic seizures

L: left; R: right; BT: bitemporal; BT>L, bitemporal with left sided predominance; BT>R: bitemporal with right sided predominance

HA: hippocampal atrophy; BHA: bilateral hippocampal atrophy, >L: left sided predominance; >R: right sided predominance.

AM: amygdala.

*** also had right hemispheric atrophy.

MTS: mesial temporal sclerosis; NSA: no significant abnormality; NA: not available (see text for more details). NR: not recorded.

Legends for figures:

Figure 1: Coronal T1-IR and T2 weighted images from patient # 19 on table 1; showing classical MRI signs of mesial temporal sclerosis: reduced volume and hyperintense T2 signal in right amygdala and hippocampus. Note the abnormal internal structure, with hypointense T1 and hyperintense T2 signal in right hippocampus.

Figure 2: Histological specimem (HE coloration) from patient #19 (MRI shown in figure 1), showing typical neuronal loss (white arrow) and gliosis (black arrow) on CA1, CA3 and dentate gyrus (indicated by the star). The available fragments containing CA2 showed no significant abnormalities (not shown in the figure).

Pt. #	Age	Sex	Risk Factors	Onset (years)	Seizure types	Aura	Ictal EEG	Interictal EEG	MRI	amygdalar atrophy	Hyperintense T2 signal	Surgery	Pathology	Follow up	Engel's scale
1	24	M	HT @ 5m	0,5	SPS-CPS	epigastric discomfort	LFT	BT>L	LHA	yes	yes	LSAH	MTS Mild-Mod	8y4m	Ib
2	21	F	CFS @ 1y*	1	SPS-CPS	feeling in her throat	BT>R	BT>R	RHA	yes	yes	RSAH	NSA	8y3m	Ia
3	33	M	FS @ 2y	2	SPS-CPS	feeling of heavyness	RT	RT	RHA	yes	yes	RSAH	MTS Sev	8y8m	Ib
4	46	M	FS @ 14m	2	SPS-CPS	sexual	NR**	RT	RHA***	yes	yes	RSAH	MTS Sev	9y7m	Ia
5	31	F	FS @ 10m	8	SPS-CPS	sees herself watching the surrounds, epigastric sensation	BT>L	BT>L	LHA	yes	yes	LTL	MTS Mod-Sev	9y10m	Ib
6	45	F	no	0,25	SPS-CPS	pressure on head + "jamais vu"	BT>L**	BT>L	normal	no	no	LTL	NSA	4y9m	II
7	42	M	CFS @ 1y	10	SPS-CPS	coughs and feels lost, strange feeling in head	BT>R	BT>R	BHA>R	no	yes	RSAH	MTS Mild-Mod	1y8m	I
8	52	F	no	7	SPS-CPS-GTCS	fear	BT>L**	BT>L	BHA>L	yes	yes	LTL	gliosis parahippoc and AM	7y1m	Ia
9	29	F	no	14	CPS-GTCS	strange feelings inside, evolving into intense fear	BT>R	BT>R	normal	no	no	RSHA	mild AM and end folium sclerosis	7y11m	IV
10	46	M	CFS @ 16m	1	SPS-CPS-GTCS	epigastric discomfort	RT**	RT	RHA	yes	yes	RTL	MTS Mod-Sev	8y5m	Ia
11	42	M	no	2	SPS-CPS-GTCS	epigastric discomfort	LT	LT	LHA	no	yes	LTL	NA	4y8m (1y8m since reop)	III; I since reop
12	31	M	no	2	SPS-CPS-GTCS	epigastric discomfort	LT	BT>L	LHA	yes	yes	LTL	NA	5y	Ia
13	39	M	no	7	SPS-CPS	epigastric discomfort	RT	RT	RHA	yes	yes	RTL	NA	4y7m	Ic
14	35	F	no	8	SPS-CPS-GTCS	fear, experiential, "déja vu"	RT	BT>R	RHA +RTcysts	no	yes	RTL	MTS Mild-Mod	4y6m	Ia
15	45	F	no	1	SPS-CPS-GTCS	strange feeling	LT	LT	LHA	yes	yes	LTL	MTS Mild-Mod	4y	Ia
16	37	F	no	8	SPS-CPS-GTCS	epigastric discomfort	LT	LT	LHA	no	yes	LTL	NA	3y7m	Id
17	37	F	no	12	SPS-CPS-GTCS	burning sensation over body	LT	LT	LHA + RT cysts	yes	yes	LTL	NA	3y4m	Ia
18	40	M	no	6	SPS-CPS-GTCS	epigastric discomfort	LT	LT	LHA	yes	yes	LTL	NSA	2y7m	Ib
19	19	F	no	1	SPS-CPS	epigastric discomfort	RT	RT	RHA	yes	yes	RTL	MTS Mild-Mod	2y	Ia
20	46	M	no	4	CPS-GTCS	no	RT	RT	BHA>R	yes	yes	RTL	NSA	2y	III

Figure 1

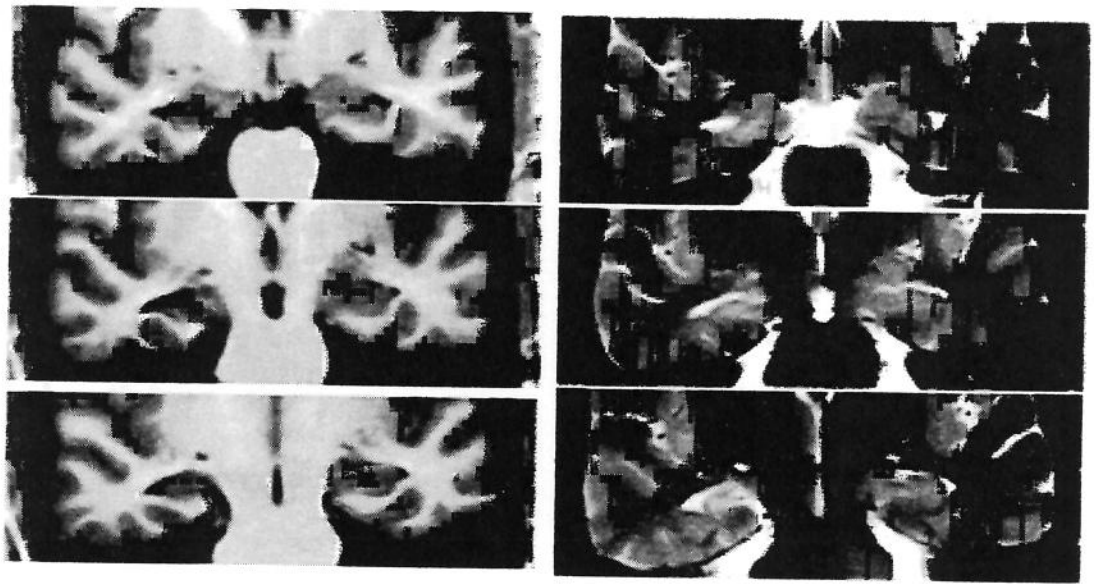
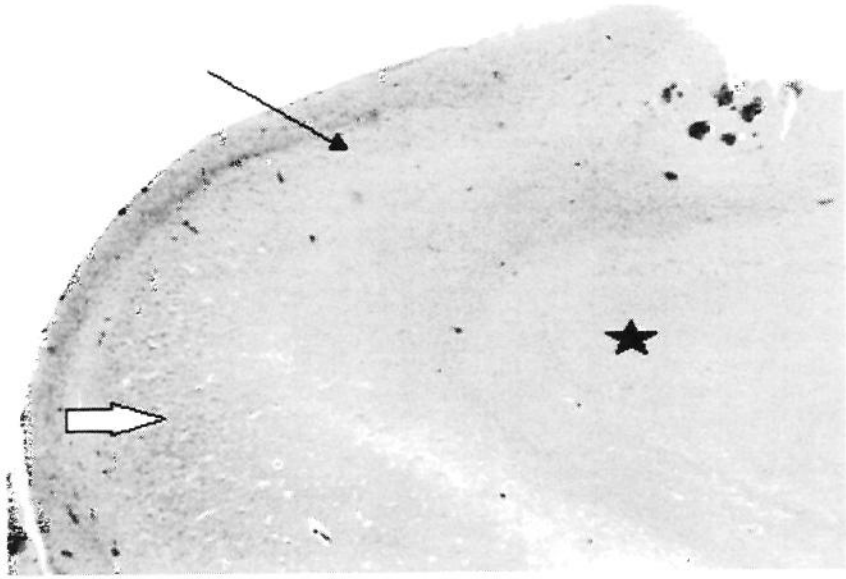


Figure 2



Artigo 6

Relevance of hippocampal atrophy and seizure frequency on memory impairment in patients with familial mesial temporal lobe epilepsy

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Relevance of hippocampal atrophy and seizure frequency on memory impairment in patients with familial mesial temporal lobe epilepsy

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Key words: hippocampal atrophy; seizure frequency; memory deficits; familial MTLE

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ABSTRACT

Background: Hippocampal atrophy (HA) is frequent in familial mesial temporal lobe epilepsy (FMTLE), both in individuals with benign and refractory epilepsy.

Objective: To correlate HA with memory performance in patients with benign and refractory FMTLE.

Design/ Methods: We studied 30 patients with FMTLE (16 with refractory and 14 with benign epilepsy). Neuropsychological evaluation included Wechsler Adult Intelligence Scale – Revised, Edinburgh Handedness Inventory, Dichotic Listening Test, Verbal Fluency Test, Boston Naming Test, Strub & Black Vigilance Test, Trail Making Test, Winsconsin Card Sorting Test and Wechsler Memory Scale – Revised. Hippocampal volumetry was performed in all patients for determination of HA.

Results: Seizure control did not determine differences in age, education level, handedness dominance, vigilance, attentional, executive, language or visual memory functions. However, patients with refractory seizures had lower IQ ($p=0.037$), worse delayed recall ($p=0.022$), general ($p=0.026$) and verbal ($p=0.025$) memory. HA was associated with more deficits of general memory ($p=0.019$) and delayed recall ($p=0.009$) and immediate recall of a word list ($p=0.03$). Left HA was associated with deficits of general memory ($p=0.026$), verbal memory ($p=0.030$) and delayed recall ($p=0.019$). Bilateral HA was related to visual memory deficits ($p=0.022$).

Conclusions: Left HA affected general and verbal memory, as well as delayed recall. Deficit of visual memory occurred only in bilateral HA. Refractory seizures and HA related to memory impairment in patients with FMTLE. HA was associated with memory-specific deficits independent of seizure frequency. However, frequent seizures potentiated the effect of HA on memory impairment.

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) is related to hippocampal atrophy (HA), associated with other signs of mesial temporal sclerosis (MTS) [1], and memory deficits [2]. The classic material-specific model of memory predicts that resection of the left hippocampus implicates in deficits of verbal memory [3,4,5,6] and resection of the right hippocampus, in deficits of visual memory [7,8,9]. However, more recent studies [2,10-17] have shown that the relationship between side of hippocampal pathology and memory function is more evident in patients with left HA than in patients with right HA. Besides etiology, other factors seem to be involved in memory impairments of these patients, such as age of seizure onset [18,19,20,21], duration of epilepsy [22,23,24], seizure frequency, and use of antiepileptic drugs (AED) [25,26].

Familial mesial temporal lobe epilepsy (FMTLE) is a well-characterized syndrome [27,28,29]. Although the majority of affected subjects have a benign clinical course, including individuals with a single seizure episode in life, MRI signs of MTS is frequent [27]. These clinical-MRI data indicate a genetic factor determining the development of hippocampal pathology. The differences in seizure frequency may be due to the interaction of modifying factors, both genetic and environmental [27,29].

Studies have shown that patients with HA present with memory impairment [2,13,14,16,17]. However, these studies include only patients with frequent and refractory seizures who are candidate for surgical treatment. Therefore, the differential role of HA and seizures themselves is difficult to be determined.

The finding of HA in individuals with rare seizures and remission in one end, and refractory epilepsy in the other end of the spectrum of FMTLE, provides an unique opportunity to investigate the additional contribution of seizure frequency in memory deficits in patients with HA.

A comprehensive neuropsychological study with quantitative analysis of memory function in patients with FMTLE has not been reported yet. Identification of relationships between clinical features, HA, and neuropsychological data can contribute to better understanding of phenotype distribution in these familial cases and how they might relates with the sporadic patients.

In this study, we report the results of neuropsychological evaluation of 30 patients with FMTLE, with regard to the clinical features of the epilepsy and to the presence, degree and lateralization of HA.

PATIENTS AND METHODS

Ascertainment of subjects: In this study we include patients followed at our epilepsy clinic with the diagnosis of FMTLE, and already investigated with clinical, genetic and MRI protocols [27].

FMTLE was defined when two or more individuals in the same family presented with the diagnosis of MTLE. Most families had an average of 5 affected individuals. The diagnosis of MTLE was based on clinical and EEG findings [27]. Clinical criteria included: history of simple partial or complex partial seizure, or both, with characteristics of mesial temporal lobe origin and no suggestion of any other partial epilepsy syndrome. EEG criteria were: presence of interictal epileptiform discharges over mid-inferomesial temporal regions and no clear-cut epileptiform abnormalities elsewhere. Normal interictal EEGs did not exclude the diagnosis of MTLE.

Patients who fulfilled clinical-EEG criteria for MTLE were divided in two groups, according to seizure outcome:

- Group 1: patients with benign MTLE, evolving with remission (seizure-free for at least two years, off medication), or with good seizure control (patients on medication, with fewer than three complex partial seizures (CPS)/year. Patients who had up to 2 secondary generalized seizures/year, clearly related to abrupt withdraw of antiepileptic drugs, but who had complete seizure control on medication, were also considered as "with good seizure control".

- Group 2: patients with refractory MTLE (poor control of seizures in spite of adequate medication).

Neuropsychological Evaluation: We used Wechsler Adult Intelligence Scale – Revised (WAIS-R), Edinburgh Handedness Inventory, Dichotic Listening Test, Verbal Fluency Test (category: animal), Boston Naming Test (BNT), Strub & Black Vigilance Test, Trail Making Test (TMT), Winsconsin Card Sorting Test (WCST) and Wechsler Memory Scale – Revised (WMS-R) [30-38] , as well as tests of visual memory (immediate and delayed multiple choice recognition of ten abstract designs) and verbal learning (immediate and delayed recall of a list of ten unrelated words presented orally in ten attempts) [39].

MRI studies: MRIs were performed in a 2T scanner (Elscint Prestige®), with T1 and T2 weighted acquisitions in three orthogonal planes. In addition, a T1-weighted 3D gradient echo acquisition was obtained for multiplanar reconstruction.

Volumetric studies were performed using coronal IR images. Hippocampal formations and total intracranial volumes were manually delineated using the NIH image program, and anatomic guidelines were obtained from a standard protocol [40].

For determination of normal parameters, hippocampal volumes were obtained in a group of 30 healthy volunteers. We calculated the absolute volumes for each hippocampus. Values below two standard deviations from the mean of control group were considered abnormal.

Statistical analysis: All variables that could somehow influence the neuropsychological performance were analyzed: age at seizure onset, epilepsy duration, use of AED, presence and degree of HA. To assess differences in the distribution of these variables in each group of patients, we performed ANOVA (for continuous variables) or Chi-square test.

We used Pearson's coefficient to assess correlations between results of memory tests (visual, verbal, and general memory) and hippocampal volumes transformed into Z-scores (number of standard deviations from the mean of control group).

RESULTS

We evaluated 30 FMTLE patients (22 women, 8 men) with mean age of 33 years (range: 18-64 years), educational level of 7 years (range:1-11 years), and mean estimated IQ of 91 (66-103).

Fourteen individuals have had few seizures in life (group 1). Twelve had clinical-EEG criteria for MTLE and five of them have been seizure free for more than 5 years and are off medication now, except one who has been seizure free for 3 years and decided to continue with AED. The remaining two individuals had only febrile seizures in childhood. Sixteen patients had refractory MTLE (group 2).

Patients with refractory epilepsy showed earlier seizure onset ($p=0.04$), used greater number of AED ($p<0.01$), and tended to have longer duration of epilepsy (though not statistically significant). Fifteen patients with refractory seizures had undergone treatment with polytherapy, and only one in monotherapy. On the other hand, 8 patients with benign seizures were on monotherapy and 5 were not using any AED ($p<0.01$), including the 2 who had only febrile seizures.

Age and educational level were similar in both groups (of benign and refractory epilepsy), as well as the results of Edinburgh Handedness Inventory, Dichotic Listening, Verbal Fluency, BNT, Strub and Black Vigilance Test, TMT, WCST, and visual memory tests (both WMS-R and immediate and delayed recognition of designs). However, patients with refractory seizures had lower IQ ($p=0.037$) and inferior performance in tests of general memory ($p=0.026$), verbal memory ($p=0.025$) and delayed recall ($p=0.022$) of the WMS-R, as well as in immediate ($p=0.04$) and delayed ($p=0.03$) recall of word list.

In WMS-R test battery, 18 patients had no memory deficits [12 (67%) of these patients had benign, and 6 (33%), refractory epilepsy]. On the other hand, among the remaining 12 patients with memory deficits, 10 (83%) had refractory seizures and only 2 (17%) had good seizure control ($p=0.007$).

Volumetric studies performed in 28 patients showed mean Z score of –2.28 (-5.62 to 2.2) for left and of –2.27 (-8.02 to 2.02) for right hippocampus. HA was identified in 24 patients, of which 10 had left HA, 6 right HA and 8 bilateral HA. Visual and volumetric analysis were normal in 6 patients.

In these 24 patients with HA, the epilepsy was benign in 9 and refractory in 15. Among patients with normal hippocampal volumes, 5 (83%) had good seizure control and only one (17%) had refractory seizures (p=0.044).

Patients with HA had more deficits of general memory (p=0.019) and delayed recall (p=0.009) and immediate recall of a word list (p=0.03) than those with normal hippocampal volumes. They also had more deficits of WMS-R verbal and visual memory, and delayed recall of word list, although without reaching statistical significance, probably due to the small sample size.

Correlation between hippocampal volumes (left HA, right HA, bilateral HA) and memory scores revealed that unilateral right HA was not associated with deficits in any of memory tests. On the other hand, left HA was associated with lower scores of general memory (p=0.026), verbal memory (p=0.030) and delayed recall (p=0.019) of WMS-R, and immediate (p=0.02) and delayed (p=0.01) recall of word list. Only patients with bilateral HA tended to show lower scores on visual memory, which were statistically significant in WMS-R tests (p=0.022), but not in recognition of designs.

DISCUSSION

We compared memory performance between patients with refractory FMTLE and benign FMTLE. Both groups were similar in age, educational level, handedness and hemispheric dominance for language. We found no difference in vigilance, attentional, executive and linguistic functions, and visual memory between the two groups. Patients with refractory seizures had lower IQ and worse performance in delayed recall, general and verbal memory. In addition, patients with refractory FMTLE had earlier age of seizure onset, higher seizure frequency, and used greater number of AED than patients with benign FMTLE.

We found HA in all but one patient with refractory FMTLE but also in 9/14 (64%) with well controlled seizures or with seizure remission (benign FMTLE). This finding allowed us to investigate further the relationships among HA, severity of seizures

and memory dysfunction. Patients with HA had significantly more severe memory deficits than those with normal hippocampi. Even patients with HA and good seizure control or seizure remission had significantly more severe memory deficits than patients without HA with similar seizure profile. Those with HA and refractory seizures had significantly worse memory performance.

Moreover, we found a correlation between degree of left HA and deficits of delayed recall, general and verbal memory, but not of visual memory. There was no significant association between right HA and tests used here to evaluate verbal and visual memory. Although these findings differ from the classic material-specific memory model, they agree with more recent studies of patients with TLE undergoing evaluation for surgical treatment [2,11-17]. In these studies, there is no strong relationship between right HA and deficits of visual memory, possibly because (1) the visual memory tests employed are not robust enough to show lateralization of HA or the epileptogenic focus; or (2) visual memory has a more diffuse and bilateral representation in the brain [17]. We believe that a combination of these two hypothesis is more plausible. We have found that many patients make use of a verbal strategy to memorize a visual content. In addition, we have seen that, although right HA was not correlated with deficits of visual memory, bilateral HA was able to produce such deficits.

In conclusion, refractory seizures and HA are related to memory impairments in patients with FMTLE. Individuals with HA who are seizure-free or have had few seizures in life have significant memory-specific impairment on neuropsychological evaluation, demonstrating the independent role of HA in memory dysfunction. In addition, we demonstrated that frequent seizures potentiate the effect of HA on memory deficits in these patients.

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Artigo 7

Anterior temporal lobe structure is preserved in patients with familial mesial temporal lobe epilepsy associated with hippocampal damage

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submitted

Anterior temporal lobe volume and structure is preserved in patients with familial mesial temporal lobe epilepsy associated with hippocampal atrophy

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ABSTRACT

Introduction: Hippocampal atrophy (HA) in mesial temporal lobe epilepsy (MTLE) is frequently associated with atrophy of other structures. In Familial MTLE (FMTLE) with HA, it is not known if the genetic basis leads to more widespread abnormalities.

Objective: To determine if HA in patients with FMTLE is associated with abnormal structure and atrophy of anterior temporal lobes.

Methods: We performed visual and quantitative analysis of T1 and T2-weighted MR images, with determination of hippocampal volumes (HcVs) and anterior temporal lobe volumes (TLVs).

Results: A total of 150 FMTLE individuals, 30 refractory non-familial MTLE patients, and 30 healthy controls were studied. Despite the high frequency of HA in affected FMTLE patients (81.4%, anterior temporal lobe atrophy (ATLA) was identified in only 13.7%, similar to refractory non-familial MTLE patients (10%). The presence of ATLA did not associate with worse seizure control and abnormalities outside the mesial portion of temporal lobes were rarely seen in both familial and non-familial patients.

Conclusion: ATLA was found only in 13.7% of affected individuals. Mild structural abnormalities were restricted to the mesial temporal regions except in four patients (3.7%) with FMTLE. The frequency of ATLA and pattern of structural abnormalities were similar in FMTLE (13.7%) and non-familial MTLE patients (10%).

INTRODUCTION:

Mesial temporal lobe epilepsy (MTLE) is frequently associated with mesial temporal sclerosis (MTS) (Hauser, 1992; Gloor, 1991), which can be identified by magnetic resonance imaging (MRI) as hippocampal atrophy (HA) associated with abnormal signal intensities (Jackson et al, 1990; Berkovic et al, 1991; Watson et al, 1997). Pathological and MRI studies on refractory MTLE patients have also described reduced volumes and abnormal structural findings outside the mesial temporal regions (Cendes et al, 1993; Jack et al, 1990; Lencz et al, 1992; Lee et al, 1995; Marsh et al, 1997; Briellmann et al, 1998; Breier et al, 1996). It is supposed that more severe HA is associated with more refractory seizures and more widespread abnormalities.

Positive family history of epilepsy is frequently observed among patients with MTLE. However, these families cannot be included in only one group, and the detailed characterization of other affected family members is determinant for definition of a familial epilepsy syndrome. Patients with TLE can be found in familial TLE with auditory features (Otman et al, 1995; Poza et al, 1999; Winawer et al, 2002) that is a lateral form of TLE, in generalized epilepsy with febrile seizure (FS) plus syndrome (Singh et al, 1999) where we can observe patients with partial epilepsy (including TLE), generalized epilepsy and atypical FS, in familial partial epilepsy with variable foci (Scheffer et al, 1998), with other affected individuals presenting other partial epilepsy syndromes, and finally, familial MTLE (independently of the presence and type of hippocampal abnormalities) (Berkovic et al, 1996; Cendes et al, 1998; Kobayashi et al, 2001a).

Familial MTLE is defined when at least two first-degree relatives in a family have clinical-EEG criteria for MTLE, with no suggestion of extra-temporal seizures in any family member, as well as no evidence by clinical-EEG findings of lateral TLE (Kobayashi et al, 2001a). The majority of affected individuals have a benign clinical presentation, but some patients may have poor seizure control (Cendes et al, 1998; Kobayashi et al, 2001a). Although hippocampal atrophy (HA) was more frequent and more severe in those patients with refractory seizures, it was also observed in patients with good outcome, and even in asymptomatic family members (Kobayashi et al, 2001b; Kobayashi et al, 2002). These are strong indicators that genetic factors play a role in the genesis of hippocampal pathology in

patients with familial MTLE. It is not known if this genetic background would imply in a more widespread abnormality.

The objectives of this study were to evaluate the presence of ATLA, through the determination of temporal lobe volumes (TLVs); to assess the correlation of TLVs and hippocampal volumes (HcVs) and to correlate the presence of ATLA and HA to clinical phenotype.

PATIENTS and METHODS:

Ascertainment of individuals and control group:

We studied two groups: Familial MTLE patients and MTLE patients with no family history of epilepsy.

Familial MTLE was defined when at least two individuals (first- or second-degree relatives) had a clinical-EEG diagnosis of MTLE. Exclusion criteria were: any affected family member with partial epilepsy with extra-temporal pattern, or indicative of lateral temporal lobe epilepsy; families that could not be adequately investigated, even if two individuals had diagnosis of TLE. We evaluated all available individuals from 30 unrelated families. Affected subjects, as well as asymptomatic first-degree relatives of family members that had clinical-EEG criteria for MTLE, underwent our MRI protocol, after signing an informed consent. Familial MTLE patients were divided into 4 groups: benign MTLE (up to 3 complex partial seizures/year), refractory MTLE, other seizure types, and unaffected subjects.

A group of 30 randomly selected refractory MTLE patients were studied for comparison, all of them with no family history of epilepsy. A control group composed by 30 healthy adult volunteers (from our laboratory) was used for determination of normal parameters.

MRI study: MRIs were performed in a 2T scanner (Elscint Prestige®, Haifa, Israel), with T1 and T2 acquisitions in three orthogonal planes. MRI acquisition parameters were: (1) Sagital T1 spin echo, 6mm thick, flip angle= 180°; repetition time (TR)=430, echo time (TE)=12, matrix 200X350, field of view (FOV)=25X25cm; (2) Coronal images,

perpendicular to long axis of hippocampus, defined on the sagital images: (a) T2-weighted and proton density "fast spin echo" (FSE), 3mm thick, flip angle= 160°; TR=4800, TE=108/18, matrix 256X256, FOV=22X22cm; (b) T1-weighted inversion recovery (IR), 3mm thick, flip angle=200°; TR=2800, TE=14, inversion time (TI)=840, matrix 130X256, FOV=16X18cm; (3) Axial images parallel to the long axis of the hippocampi: (a) T1-weighted gradient echo, 3mm thick, flip angle=70°, TR=200, TE=5, matrix 180X232, FOV=22X22 cm; (b) T2-weighted FSE, 4mm thick, flip angle=120°, TR=6800, TE=129, matrix 252X328, FOV=21X23cm; (4) T1-weighted 3D gradient echo with 1mm isotropic voxel, acquired in the sagital plane for multiplanar reconstruction (1mm thick, flip angle=35°; TR=22, TE=9, matrix 256X220, FOV=23X25cm).

Visual analysis was performed in a workstation (OMNIPRO®), with careful evaluation of integrity of temporal lobe structures, specially gyri pattern, white-gray matter distinction and signal intensity. We analyzed separately the anatomy and signal intensity in the mesial portion of temporal lobe (defined here as all structures medial to the fusiform gyrus) and basal-lateral temporal areas.

For volumetry, we used a T1-IR coronal acquisition. Volumetry was performed by manual delineation of temporal lobes and hippocampi, using NIH Image Program ®. For TLVs, we included the boundaries of cortical surface from the temporal lobes, from the first slice with the temporal poles finishing at the slice where we could identify the *crura fornix* (figure 1). Hippocampal volumetry was performed according to anatomic guidelines from a standard protocol (Watson et al, 1992). Values were corrected by the variation in the total intracranial volume, which was also manually delineated from the temporal poles to the last segmented slice, excluding the brain stem.

We determined the TLVs and HcVs, as well as the asymmetry index (AI), for each subject. Atrophy was defined for values below two standard deviation from the mean of control group.

Statistical analyses: For statistical analyses we used SYSTAT9 ®. We used analysis of variance (ANOVA) to assess differences in volumes between affected and unaffected family members. Frequency of ATLA among groups was evaluated by the

Fisher's and Chi-square tests. For correlation of TLVs and HcVs we used Pearson's simple correlation or regression analysis.

RESULTS:

A total of 180 individuals were studied: 150 Familial MTLE individuals from 29 unrelated families (102 affected -18 with refractory seizures- and 48 unaffected) and 30 non-familial refractory MTLE patients.

1. Familial MTLE individuals:

Visual analysis of T1 and T2 images showed ATLA in 15/102 (14.7%) affected individuals: 6 unilateral (4 right) and 9 bilateral. Other abnormalities were seen in 4/108 (3.7%) patients: left temporal lobe hypogenesis associated with aracnoyd cyst, left temporal lobe dysmorphic features with predominance in the superior temporal girus (figure 2), left temporal lobe small encephalocele and gliotic lesion in right temporal lobe white matter anterior to the amygdala. Abnormalities in parahippocampal gyrus, fusiform gyrus and collateral sulcus accompanying HA or abnormally shaped and oriented hippocampus were identified in 12 (11%) patients (figure 3).

Only one unaffected family member (65 years old) had visually detected ATLA, but it was symmetrical bilateral, and associated with diffuse brain atrophy and hyperintense T2 signal subcortical lesions. Abnormalities within the mesial temporal regions (7 left, 1 right, 1 bilateral) were seen in 9/48 (18.7%) asymptomatics, all with ipsilateral abnormal shape and axis of hippocampal formation.

Quantitative analysis: Among the 102 affected individuals, ATLA was observed in 14 (13.7%) (2 bilateral) and HA was present in 83 (81.4%) patients. In the group of 48 asymptomatic family members, ATLA was identified in 3 (6.2%) individuals (1 bilateral) and HA in 15 (31.2%).

Overall, ATLA in familial patients was most commonly unilateral (14 unilateral and 3 bilateral) and was not associated with poorer seizure control, as only 2 of these familial patients have refractory seizures. HA was identified in 82/102 (80.4%) affected individuals and 15/48 (31.2%) asymptomatics. HA was observed in 100% of refractory Familial MTLE patients, and this was more frequent than in non-familial patients (Chi-square, p=0.013).

2. Non-familial refractory MTLE patients:

Visual analysis showed ATLA in 7/30 (23%) patients and small hyperintense white matter lesions in the temporal lobes in 5/30 (17%) patients. Abnormalities in the mesial temporal portion were observed in 3/30 (10%) patients, with altered collateral sulci and enlarged adjacent cortex (2 bilateral, 1 left).

Volumetry identified ATLA in only 3/30 (10%) patients with refractory non-familial MTLE, whereas HA was identified in 20 (66.6%).

3. Statistical analyses:

Correlation analyses showed that TLVs were associated with ipsilateral HcVs (r^2=0.092, p<0.0001) and with contralateral hippocampus (r^2=0.028, p=0.0001), although less than 10% of the variance in TLVs could be related to the HcVs, as indicated by the r^2 values. Patients with ATLA had significantly smaller HcV AI , as compared to those with normal TLVs (ANOVA, F=3.063, p<0.0001).

There was no difference in TLVs between affected and unaffected family members (ANOVA, p=0.1, for right and left sides). Although patients with refractory seizures had smaller HcV Zscores as compared to patients with benign clinical course (ANOVA, p=0.03 for right and p=0.02 for left), no such difference was observed in TLV Zscores (ANOVA, p=0.48 for right and p=0.30 for left).

We assessed severity of atrophy in affected and unaffected subjects, from both hippocampi and temporal lobes, by the AI. Although no difference was found regarding the temporal lobes AI (ANOVA, $F(1)=2.770$, $p=0.09$), there was a significant difference in the hippocampal AI (ANOVA, $F(1)=1.028$, $p=0.001$).

There was no difference in frequency or degree of ATLA between patients with familial and non-familial refractory MTLE (ANOVA, $p=0.6$).

DISCUSSION:

Abnormalities of the temporal lobes can co-exist with more common pathological findings such as MTS. Temporal lobe developmental malformation (TLDM) have been referred to as a form of temporal lobe cortical dysgenesis usually associated with abnormal MRI signal in the white matter of temporal pole (Kuzniecky et al, 1991; Kuzniecky et al, 1994; Hoo et al, 1998). TLDM was found in about 10% of MTLE patients who underwent anterior temporal lobectomy for refractory seizures and MRI diagnostic criteria have been determined (Kuzniecky et al, 1991; Kuzniecky et al, 1994). These criteria include the presence of abnormal gray-white matter pattern involving the anterior 4 to 5 cm of the temporal lobe (on T2-weighted images, and IR and FLAIR sequences) and abnormal gyral thickening of the temporal neocortex associated with hyperintensity on T2-weighted images.

In a series of 30 patients with TLDM, there was associated atrophy of the anterior temporal lobe in 33% and HA determined by volumetry was identified in 86% (Hoo et al, 1998). In 24 patients the developmental malformation was confined to either one or two temporal gyri, with the middle and inferior temporal gyri most frequently involved (Hoo et al, 1998).

In Familial MTLE, HA with abnormal internal signal is observed in patients with well-controlled epilepsy and also in asymptomatic individuals. These are indicative of a pre-existing structural abnormality, which is not always associated with refractory seizures and must be determined by genetic factors (Kobayashi et al, 2001a; Kobayashi et al, 2001b; Kobayashi et al, 2002).

In this study, a careful visual inspection of the temporal lobes using multiplanar reconstruction revealed that in the few patients with temporal lobe abnormalities, these were restricted to the mesial portion and were considered mild developmental abnormalities quite different from the pattern of TLDM. Clear-cut signs of dysplasia (thick, blurred and hyperintense cortex or white-gray matter transition) were not observed. Abnormalities on signal intensity outside the context of a widespread cerebrovascular disease were not observed.

There was no difference in frequency of temporal lobe abnormalities or TLVs between patients with and without family history of epilepsy. The genetic factor associated with the development of hippocampal pathology in Familial MTLE does not imply in a more widespread abnormality in the temporal regions. Abnormalities were observed in the mesial portion, and volume reduction of temporal lobes was rare.

ACKNOWLEDGEMENTS:

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LEGENDS FOR FIGURES:

Figure 1: Boundaries for determination of temporal lobe volumes, from the first slice (at left) showing the temporal poles throughout the temporal lobes until the identification of the *crura fornix* (at right). Volumes are corrected by the variation in total brain volume.

Figure 2: Dysmorphic features observed on the left temporal lobe from one patient with Familial MTLE, with abnormal orientation of superior temporal gyrus (arrow). Note that left hippocampus has abnormal shape and axis, and the fusiform gyrus (small arrow) is thickened.

Figure 3: Abnormalities in the mesial temporal region, including the parahippocampal and fusiform gyri and the collateral sulcus (large arrow) in one patient with benign FMTLE and ipsilateral rounded hippocampus (small arrow).

Figure 1

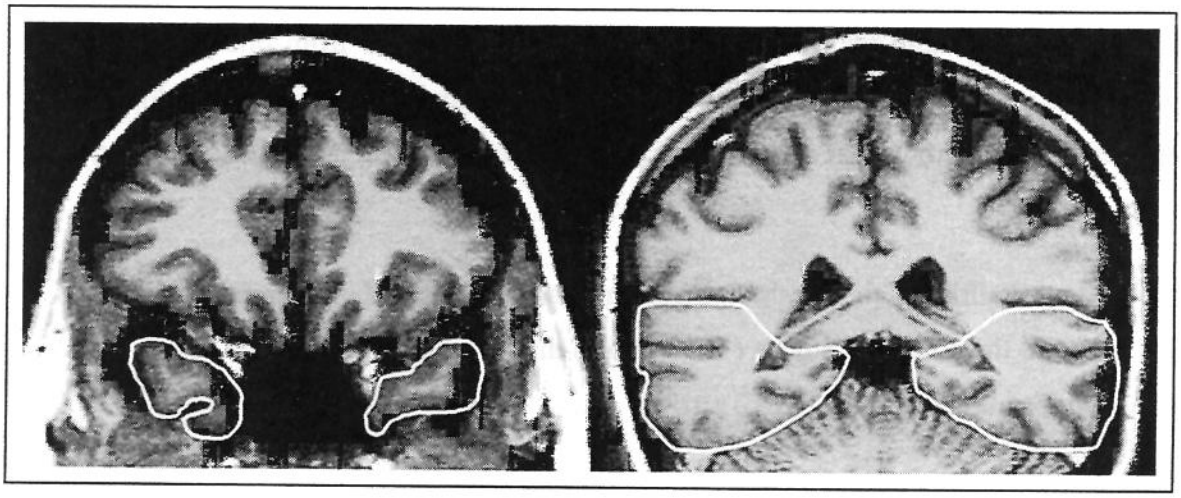


Figure 2

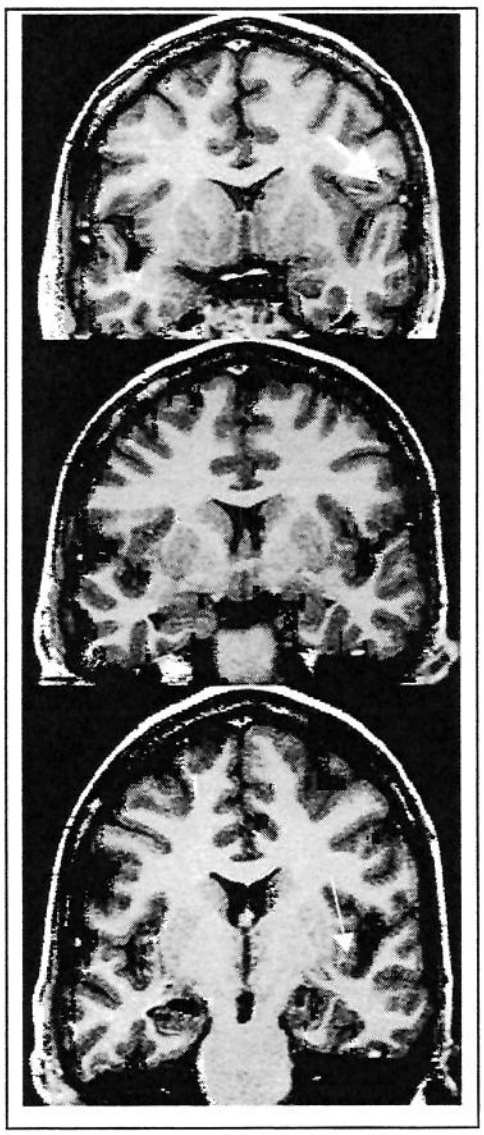
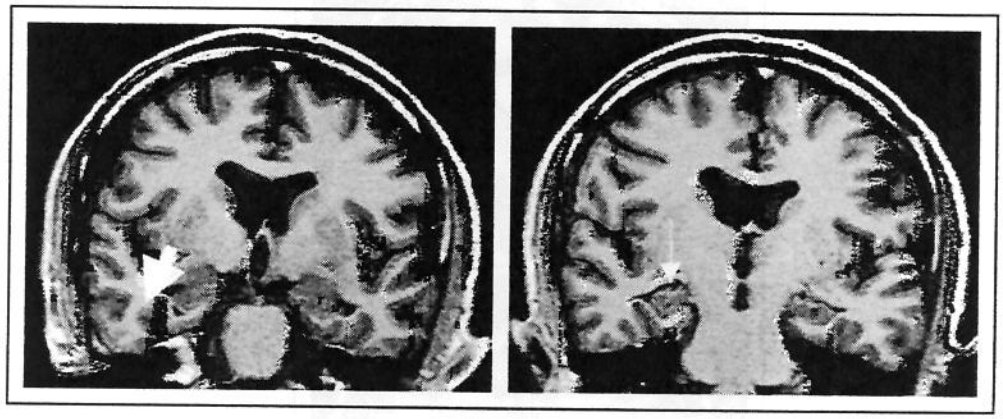


Figure 3



Artigo 8

MRI abnormalities in familial temporal lobe epilepsy with auditory auras

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submitted

MRI abnormalities in familial temporal lobe epilepsy with auditory auras

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Text word count: 1506

Abstract word count: 240

Running title: MRI in familial TLE with auditory aurasKey words: temporal lobe; dysgenesis; autosomal dominant; chromosome 10q

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Abstract

Context: Two forms of familial temporal lobe epilepsy (TLE) have been described: mesial TLE (FMTLE) and TLE with auditory auras (FTLEAA). The gene responsible for FMTLE has not been mapped yet; whereas mutations in the *LGI1* (leucine-rich, glioma-inactivated 1) gene, localized on chromosome 10q (ch10q), have been found in FTLEAA.

Objective: To describe MRI findings in patients with FTLEAA.

Design/Methods: We performed detailed clinical and molecular studies, and MRI evaluation (including volumetry) in all available individuals from one family segregating FTLEAA.

Results: We evaluated 18/25 possibly affected individuals, and 13 patients reported auditory auras. In one patient auditory auras were associated with "deja-vú", in one patient with ictal aphasia, and in two patients with visual misperception. Most patients are off medication, although all of them reported sporadic auras. Two-point lod scores were positive for seven genotyped markers on ch10q and a Zmax = 6.35 was achieved with marker D10S583 at recombination fraction = 0.0. MRI was performed in 22 individuals (seven asymptomatics, three of them carriers of the ch10q haplotype). Lateral temporal lobe malformations were identified by visual analysis in 10 individuals, two of them with global enlargement demonstrated by volumetry. Mildly reduced hippocampi were observed in four individuals.

Conclusions: In this family with FTLEAA we found developmental abnormalities in the lateral cortex of the temporal lobes in 53% of affected individuals. In contrast with FMLTE, none of the affected individuals in this family had MRI evidence of hippocampal sclerosis.

Introduction

The familial occurrence of temporal lobe epilepsy (TLE) was first described as a benign clinical form of TLE[1]. MRI studies in familial mesial TLE (FMTLE) demonstrated signs of hippocampal sclerosis (HS) not only in patients with refractory seizures, but also in patients with good seizure control and seizure remission. These findings indicate a strong genetic factor for the development of HS[2,3].

Another form of familial TLE was first reported by Ottman *et al*[4] and later by other authors[5-7]. Seizure semiology pointed to an extrahippocampal epileptogenic area and characteristically most patients referred auditory auras. Patients have good seizure control, and epileptiform discharges are observed over the posterior temporal regions. Molecular studies identified linkage to chromosome 10q (ch10q)[4-7] and the gene has been recently cloned (leucine-rich, glioma-inactivated 1 gene)[8] . No MRI abnormalities were described in these patients so far[4-7].

The objective of this study was to investigate MRI abnormalities in one large kindred with familial TLE with auditory auras linked to ch10q.

Methods

We studied one large family segregating TLE with auditory auras, with detailed clinical and MRI evaluation. Molecular studies were performed in all available family members, after informed consent.

A family pedigree was obtained during a field trip when all possibly affected individuals were clinically assessed by at least one of us. Seizures and epilepsy syndromes were determined according to the ILAE recommendations and all affected individuals were classified also by the clinical outcome.

Genomic DNA was extracted from blood samples and genotyped for seven dinucleotide repeat markers (D10S583, D10S185, D10S574, D10S1680, D10S577, D10S192 and D10S566)[9], which flank the 15 cM candidate interval on ch10q. We

calculated two-point lod scores using the MLink program of the Linkage package[10] assuming an autosomal dominant inheritance with 80% penetrance.

MRI scans were performed in a 2T scanner (Elscint Prestige, Haifa, Israel), with T1- and T2- weighted images in three orthogonal planes, including thin coronal (3mm) T1 inversion recovery (IR) images, perpendicular to the long axis of hippocampus. In addition, a 3D T1 acquisition was obtained for multiplanar reconstruction (MPR).

MRI acquisition parameters were: (*1*) Sagital T1 spin echo, 6mm thick, flip angle= 180°; repetition time (TR)=430, echo time (TE)=12, matrix 200X350, field of view (FOV)=25X25cm; (*2*) Coronal images, perpendicular to long axis of hippocampus, defined by the sagital images; (*2.a*) T2-weighted "fast spin echo" (FSE), 4mm thick, flip angle= 120°; TR=4800, TE=129, matrix 252X320, FOV=18X18cm; (*2.b*) T1-weighted Inversion Recovery, 3mm thick, flip angle=200°; TR=2800, TE=14, inversion time (TI)=840, matrix 130X256, FOV=16X18cm; (*3*) Axial images parallel to the long axis of the hippocampi; (*3.a*) T1-weighted gradient echo, 3mm thick, flip angle=70°, TR=200, TE=5, matrix 180X232, FOV=22X22 cm; (*3.b*) T2-weighted FSE, 4mm thick, flip angle=120°, TR=6800, TE=129, matrix 252X328, FOV=21X23cm; (*4*) T1-weighted 3D gradient echo, acquired in the sagital plane (1mm thick, flip angle=35°; TR=22, TE=9, matrix 256X220, FOV=23X25cm).

Visual analyses were performed using a workstation (OMNIPRO®, Elscint, Haifa, Israel) for MPR. Quantitative analyses of hippocampal formation and the anterior aspect of the temporal lobes (volumetry) were done according to a standardized protocol[11], using thin coronal T1 inversion recovery images and NIH Image ® program (www.rsb.info.nih.gov/nih-image).

Volumes were compared to a control group of 20 healthy adult volunteers, and data were transformed into Zscores (number of standard-deviation from the mean of control group).

Results

We identified in the pedigree (figure 1) 26 possibly affected subjects (5 were deceased). We evaluated 18 of them: 11 men and 7 women. Mean age at seizure onset was 19, ranging from 10 to 35 years. History of risk factors (febrile convulsions, head trauma or meningitis) was negative for all evaluated individuals that had clinical criteria for TLE with auditory auras. All patients have a benign clinical course.

Auditory auras were referred by 12/18 (66%) patients, and were described as a radio sound or a motorcycle running in most of them (table 1). Other referred symptoms are listed in table 1, and included "déjà-vu", visual misperception, with distortion of faces or objects, and episodes in which they suddenly were unable to hear or understand what people said (aphasic aura). There was only one patient (III-29) who did not report auras, but she have had only few generalized tonic-clonic seizures (GTCS) during sleep. All of them had the affected haplotype on ch10q. Secondarily GTCS were reported as a rare manifestation by 12 patients. One individual (V-6) had only recurrent febrile seizures during childhood, but no clinical findings of TLE with auditory auras. He did not have the affected haplotype.

Two point lod scores were above Z=3.0 for all seven markers genotyped on ch10q table 2): Zmax=5.61 at θ =0 for D10S583, Zmax=6.35 at θ =0 for D10S185, Zmax=4.79 at θ =0 for D10S574, Zmax=4.77 at θ =0 for D10S1680, Zmax=4.26 at θ =0 for D10S577, Zmax=5.55 at θ =0 for D10S192 and Zmax=4.26 at θ =0.05 for D10S566.

Interictal electroencephalogram was performed in six patients, with no abnormalities.

Twenty-two family members underwent MRI scanning (seven asymptomatic, four of them haplotype carriers). In table 3 we show the affected status, the presence of the ch10q haplotype, the visual and the quantitative MRI studies for each subject. Visual analysis showed lateral temporal lobe dysgenetic features (figures 2 and 3) in 10/22 (45%) patients. Their left temporal lobes seemed enlarged and sometimes with an encephalocele-like feature (figure 2). However, anterior temporal lobe volumetry showed a significant global increase in volumes in only two individuals.

Altered shape and/or axis of left hippocampal formation (figure 2), associated with dysgenetic characteristics in the ipsilateral mesial temporal lobe was identified in four of these patients. Volumetric studies revealed mildly reduced hippocampi in four individuals, with Zscores ranging from –2.0 to –2.5. In two of them, altered shape and axis of mesial temporal structures and mildly increased hippocampal T2 signal was also observed on visual analysis. However, none of these four patients fulfilled the criteria for determining MRI evidence of mesial temporal sclerosis (MTS) on visual analysis, as commonly encountered in FMTLE [2].

Discussion

Although the description of auditory auras in this familial form of TLE is remarkable, some patients report also other sensory and psychic symptoms, in isolation or accompanying the auditory symptoms[12]. Auditory features may vary among affected family members, from undefined sounds to auditory illusions like distortions and volume changes. In addition, some patients presented with an ictal aphasia. All these positive and negative manifestations suggest a lateral temporal lobe seizure focus, involving the cortex of posterior temporal regions.

The identification of temporal lobe abnormalities in MRI of patients segregating this specific form of TLE, linked to ch10q, has not been reported so far. Clear cut signs of lateral temporal malformations were found in 53% of affected individuals and in one asymptomatic carrier of the haplotype. Although four individuals had mildly reduced hippocampal volumes determined by volumetry, this was not sufficient for defining MRI evidence of MTS. However, this mild volume loss and altered shape of hippocampus and parahippocampal gyrus may influence the pattern of propagation of ictal discharges and seizure semiology.

The relationship of the mesial and lateral aspects of the temporal lobe has been extensively studied [13]. Although it is well recognized that in mesial TLE the main structures implied in the pathogenesis of epilepsy are the hippocampus, amygdala and other medial

temporal lobe structures, the lateral temporal cortex may also play an important role in this scenario. The subcortical connections of mesial temporal structures are bi-directional, and include afferents from the hypothalamus, the auditory system and lower brainstem nuclei involved in viscero-sensory and gustatory functions[13].

Several types of perceptual phenomena can occur in temporal lobe seizures. Visual and auditory hallucinations and illusions are commonly elicited by temporal lobe seizure discharge. Auditory illusions are usually changes in loudness of perceived sounds. Most of these changes are attributable to discharge in auditory association cortex, but occasionally they can be reproduced by amygdaloid stimulation[14]. These illusions frequently have experiential qualities. Elementary auditory and visual hallucinations indicate discharge in the primary auditory and visual cortices. The map of Penfield and Perot's stimulation responses showed that the points in the temporal isocortex from which auditory experiential phenomena could be elicited occupy the first temporal convolution. Experiential phenomena with auditory features may be elicited by stimulation with intracranial electrodes of several temporal lobe structures[14]. These were observed with an after-discharge beyond the stimulated site in 22/75 (29%) individuals[14]. Auditory hallucinations/illusions (one with associated visual hallucination) were reported by three patients after hippocampus stimulation. Experiential phenomena without an after-discharge or with discharges limited to the stimulated site were elicited in 20/75 (27%) patients and three of them had auditory hallucinations/illusions combined with visual features (one from temporal isocortex stimulation and two from amygdala stimulation)[14].

We cannot assure that the developmental structural abnormalities in the temporal lobes found in our patients with autosomal dominant partial epilepsy with auditory aura are directly implicated in seizure origin. However, the MRI findings in this family with TLE with auditory auras are clearly distinct from the MRI findings in FMTLE, and these different abnormalities are consistent with the distinct seizure semiology in these two forms of familial TLE.

Acknowledgements

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Legends for figures:

Figure 1: pedigree from the family with temporal lobe epilepsy and auditory auras, with haplotypes

● ■ Affected individual

○ □ Asymptomatic individual

▪ Febrile seizures only

Figure 2: T1-IR coronal images from patient III-13 showing left temporal lobe dysgenesis, characterized by enlargement of the lateral temporal lobe, with small gyri (although not characterizing polymicrogyria), and absence of first and second temporal sulcus. The basolateral aspect of the temporal lobe is also abnormal, more pronounced posteriorly, suggesting features of a small temporal lobe encephalocele. The mesial structures (hippocampus, parahippocampus and fusiform gyrus) have also abnormal shape and axis, altering the configuration of the temporal horn of the lateral ventricle.

Figure 3: T1-IR coronal MRIs from patients III-4 (A) and IV-11 (B) showing left temporal lobe malformation, with disgenetic aspect of temporal gyri and enlargement of the lateral aspect of the temporal lobe.

Legends for tables:

Table 1: Different types of aura in affected family members

Table 2: Two-point LOD-scores obtained for seven markers within the candidate region for TLE with auditory symptoms.

Table 3: All 22 individuals who underwent MRI studies, with visual and volumetric data

LTL: left temporal lobe

LTLM: left temporal lobe malformation

* confirmed by volumetry

nl: normal

+: positive

-: negative

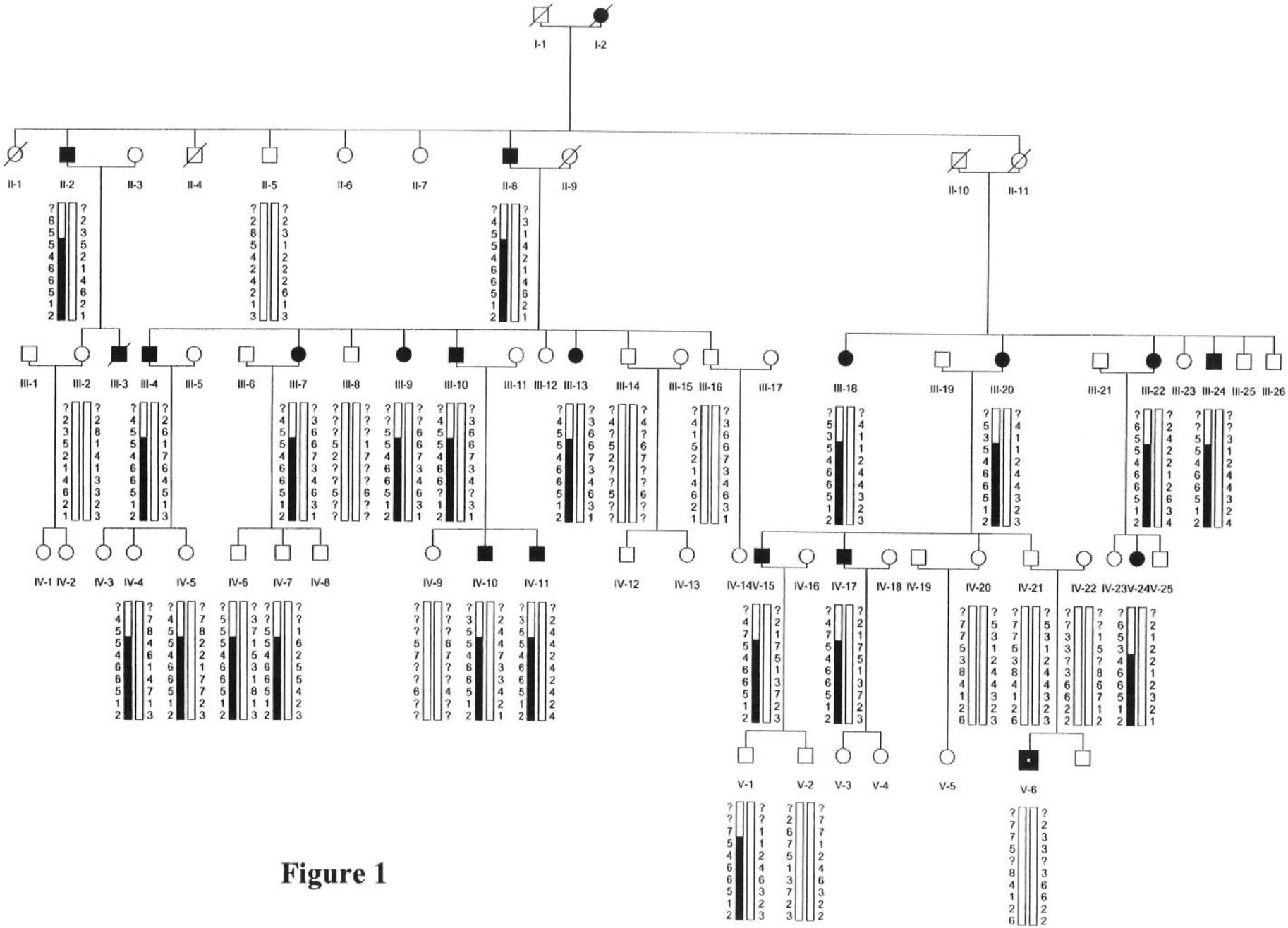
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Figure 1

Figure 2

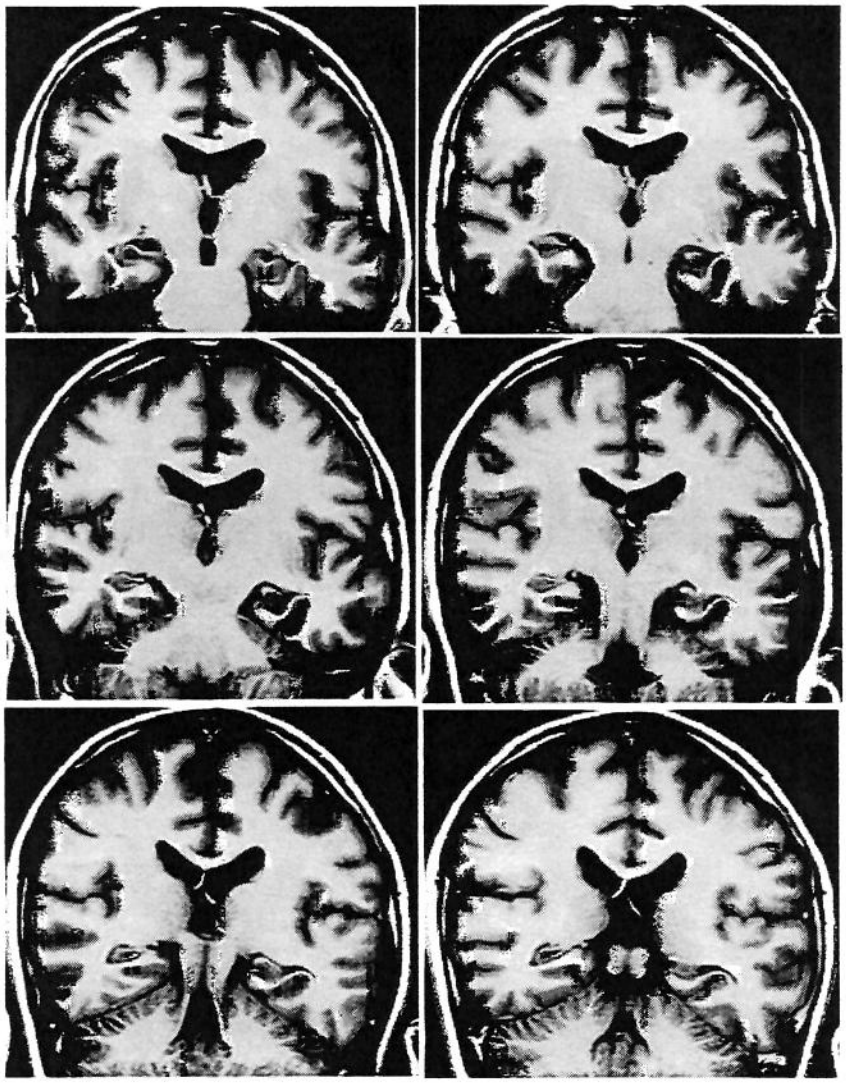
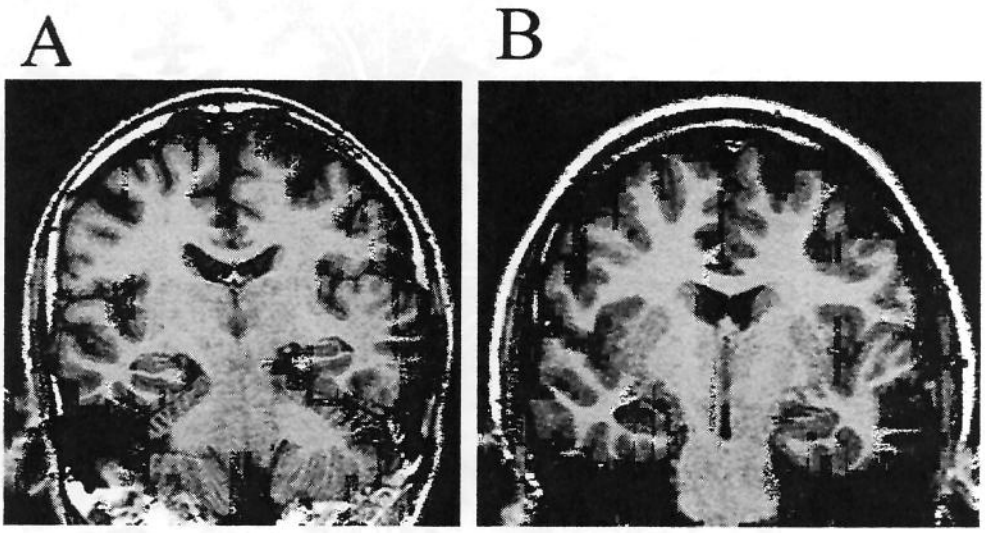


Figure 3



CAPÍTULO 4

DISCUSSÃO E CONCLUSÕES

DISCUSSÃO

O objetivo do trabalho de pesquisa apresentado nesta tese de doutorado foi determinar as características clínicas e de RM em pacientes com ELT familial. Cada um dos oito artigos apresentados nesta tese contêm discussão específica para cada tópico. Deste modo, para evitar repetições desnecessárias, apresentaremos a seguir uma breve discussão final.

A definição de ELT familial é variável na literatura. Alguns trabalhos não distinguem as formas mesial e lateral [Picard et al, 2000; Depondt et al, 2002], enquanto outros definem a ELT familial na ausência de alterações à RM [Berkovic et al, 1996]. A primeira descrição incluía ainda o critério de benignidade da epilepsia [Berkovic et al, 1994]. Quanto ao número de afetados na família, é consistentemente aceito na literatura mundial a adoção do critério de dois ou mais indivíduos afetados numa família, sendo o grau de parentesco entre eles definido em alguns trabalhos como primeiro grau e em outros como de primeiro ou segundo graus. Estas diferenças levam à exclusão ou inclusão arbitrária de várias famílias.

O critério adotado neste trabalho, para definição de ELT familial foi de dois ou mais afetados, parentes em primeiro ou segundo grau, com quadro clínico-eletroencefalográfico de ELT, sem suspeita de epilepsia parcial extratemporal em outros familiares afetados. Achamos adequado incluir parentes em segundo grau, uma vez que muitos heredogramas evidenciam penetrância incompleta, com assintomáticos portadores obrigatórios com filhos clinicamente afetados. As características das crises permitiram a divisão das famílias nas formas mesial e lateral, e a presença de alterações à RM não foi critério de inclusão ou exclusão de nenhuma família ou indivíduo.

A grande maioria dos pacientes identificados com história familiar de epilepsia parcial apresentavam ELTM (68% dos casos familiares), apesar de algumas famílias com outras formas de epilepsia parcial benigna terem sido encontradas em menor proporção (artigo #1).

Entre os pacientes com ELT (aproximadamente 450), a freqüência estimada de história familiar de epilepsia obtida até o momento foi de cerca de 10%, com grande prevalência da forma mesial. Nem todas as famílias avaliadas preenchiam o critério definido como dois ou mais parentes em primeiro ou segundo graus com diagnóstico clínico-eletroencefalográfico de ELT. Cerca de seis famílias foram excluídas do estudo por apresentarem apenas um indivíduo com ELT definitiva, ou dois indivíduos com diagnóstico de ELT porém parentes mais distantes, ou ainda outros membros da família com outra síndrome epiléptica parcial. Além disso, outras três prováveis famílias não puderam ser avaliadas por recusa dos indivíduos possivelmente afetados. Familiares falecidos com história de crises foram referidos por três pacientes, que não souberam fornecer dados semiológicos que permitissem uma hipótese diagnóstica para sua epilepsia.

Uma parte dos familiares afetados não preenchiam os critérios para ELT (CF apenas, crises únicas e CTCGs sem início parcial identificável ou durante o sono). Estes indivíduos foram também avaliados e incluídos no estudo, desde que fizessem parte de uma família com dois ou mais indivíduos com critérios para ELT. Particularmente aqueles com CTCG no sono, podem corresponder a pacientes com a forma noturna de ELTM [Bernasconi et al, 1998] e a não ser que algum familiar fortuitamente observe o início da crise, clinicamente se torna difícil determinar a ocorrência de crises parciais.

Estudamos inicialmente 98 indivíduos de 22 famílias não relacionadas com ELTMfamilial (artigo #2), com até 23 indivíduos afetados por família (média de 5). A análise dos heredogramas indicava um padrão de herança autossômica dominante com penetrância incompleta. Apesar da maioria dos indivíduos apresentar quadro benigno, crises refratárias foram observadas em 24% dos pacientes até então avaliados. Ao contrário de séries não familiares de ELTM, história de CF na infância foi identificada em apenas 6% dos pacientes.

Novas famílias foram avaliadas (atualmente são 45 famílias com ELTM e 2 com ELTL) e num estudo multicêntrico realizamos RM em 142 pacientes com ELTMfamilial. AH determinada por volumetria e alterações da estrutura interna (incluindo hipersinal nas seqüências ponderadas em T2) foi identificada em 70% dos indivíduos afetados. Apesar da AH ser mais freqüente e mais severa nos pacientes com crises

refratárias, 71% dos pacientes com AH apresentava epilepsia bem controlada ou crise única (artigo #3). Estes dados, ou seja, recorrência familiar e o padrão de segregação demonstrado nos heredogramas (anexo 4), sugerem a presença de fatores genéticos determinando o desenvolvimento da anormalidade hipocampal nestes indivíduos com ELTM familial. A análise detalhada dos heredogramas das famílias com maior número de indivíduos afetados (anexo 4) fornece evidências de um gene maior com herança autossômica dominante, que pode ser modificado por outros genes e/ou fatores ambientais. Portanto, a determinação do fenótipo (p. ex. alteração hipocampal, ocorrência e severidade de crises epilépticas, incluindo resposta às DAEs) dependeria da interação de outros fatores modificadores, tanto genéticos quanto ambientais.

Para verificar a ocorrência de anormalidades em familiares não afetados, realizamos volumetria hipocampal por RM em 52 indivíduos assintomáticos, parentes em primeiro grau de indivíduos afetados com critérios diagnósticos de ELTM. AH (redução volumétrica associada a alteração de sinal) foi observada em 34% destes indivíduos (artigo #4), sem diferença na idade atual dos indivíduos com e sem AH. Estes achados indicam que as alterações hipocampais são geneticamente determinadas e não conseqüência da ocorrência de crises.

As características clínicas, da AH à RM, e dos achados eletroencefalográficos em pacientes com ELTMfamilial e crises refratárias pareciam não diferir absolutamente do padrão observado em pacientes com o quadro clássico de ELTM refratária não-familial. Além disso, vários pacientes refratários que haviam já sido submetidos a tratamento cirúrgico, com boa evolução, tiveram sua história familiar de epilepsia adequadamente investigada e esclarecida somente após a cirurgia.

Iniciamos então, o estudo do prognóstico cirúrgico de pacientes com ELTM familial e crises refratárias conjuntamente com pesquisadores de Montreal, com análise retrospectiva destes pacientes. Observamos que pacientes com ELTM familial e crises refratárias apresentavam ótimo prognóstico após ressecção hipocampal, sendo que 85% ficaram livres de crises (artigo #5). Fatores associados a um controle incompleto das crises no pós-operatório foram volumes hipocampais normais, AH bilateral e crises bitemporais. Exame histopatológico qualitativo evidenciou achados clássicos de esclerose mesial

temporal (EMT) com vários graus de severidade de perda neuronal e gliose hipocampal, com preservação de CA2, sendo indistintos das alterações encontradas em pacientes com ELTM sem qualquer antecedente familiar de crises.

Estruturalmente, tínhamos evidências de que a AH nos pacientes familiares era semelhante à encontrada em pacientes esporádicos. Para avaliar se a presença de AH nestes indivíduos estava associada a alterações funcionais do sistema hipocampal, realizamos avaliação neuropsicológica em pacientes com diferentes graus de atrofia e severidade da epilepsia (artigo #6). Pacientes com crises refratárias tiveram pior desempenho e houve associação de déficit de memória verbal e AH esquerda. Este padrão é semelhante ao encontrado em pacientes com ELTM não-familiar. Outras alterações neuropsicológicas, encontradas em pacientes com alterações cerebrais mais difusas, não foram evidenciadas em nossos pacientes, indicando uma disfunção restrita ao sistema de memória.

Especulava-se se a existência de uma base genética determinante da AH levaria a alterações mais difusas no lobo temporal. Avaliamos a presença de atrofia na porção anterior dos lobos temporais, através de estudo volumétrico, bem como análise visual cuidadosa para identificação de alterações do padrão dos giros, transição córtico-subcortical, e sinal T2 (artigo #7). Apesar de correlação do volume hipocampal com o volume do lobo temporal, atrofia de lobo temporal foi encontrada em apenas 13,7% dos indivíduos. Análise visual cuidadosa dos lobos temporais evidenciou que as alterações presentes eram restritas às regiões mesiais, envolvendo giro parahipocampal e fusiforme. Estes achados indicam que, apesar da base genética determinar alterações hipocampais, anormalidades cerebrais mais difusas são pouco freqüentes em pacientes com ELTMfamiliar.

Apenas uma grande família com ELT e auras auditivas foi estudada até o momento, (artigo #8), sendo a boa evolução clínica encontrada em todos os pacientes avaliados. Encontramos ligação para o cromossomo 10q e atualmente estamos testando a mutação que foi recentemente descrita relacionada a este locus. Alterações à RM, compatíveis com malformação do desenvolvimento dos lobos temporais foram observadas em 45% dos pacientes. Entretanto, é impossível determinar o papel destas alterações na gênese dos fenômenos auditivos.

A ELT familial é uma síndrome provavelmente subestimada em serviços de epilepsia. Em nosso meio, aproximadamente 10% dos pacientes com ELT apresentavam história familiar de crises que permitiram o diagnóstico de ELT familial. A maior parte dos pacientes não referiu espontaneamente história familiar de crises, e ao serem questionados sobre o assunto, muitas vezes não sabiam responder. A busca ativa de informações entre os familiares mais idosos trouxe surpresa para os próprios pacientes, que desconheciam a história de crises nas suas famílias.

Além disso, a determinação da freqüência de ELT familial exige avaliação clínica detalhada dos indivíduos possivelmente afetados, uma vez que várias famílias possuíam apenas um indivíduo com critérios para ELT e portanto foram excluídas do estudo. É necessário discriminar o tipo de crise de cada familiar possivelmente afetado, fazendo distinção entre crises de origem na região mesial e lateral.

Apesar da existência de pacientes refratários ao tratamento medicamentoso, a maior parte dos pacientes com ELTMfamilial apresentava uma boa evolução clínica. Este fato esteve associado ao desconhecimento da história familiar não somente da equipe médica, mas também da própria família. As características clínicas, eletroencefalográficas, de neuroimagem e patologia disponíveis até o momento, não permitem diferenciar estes pacientes com ELTMfamilial daqueles com ELTM "isolados".

O achado de alterações à RM compatíveis com EMT em familiares assintomáticos é indicativo de que estas famílias estão segregando um ou mais genes relacionados com o desenvolvimento de alterações hipocampais. A ação de fatores modificadores, genéticos e/ou ambientais, seria determinante para que haja manifestação clínica de epilepsia.

Muitas famílias foram excluídas deste estudo por falta de evidência clínica e de EEG que permitisse identificar ao menos dois indivíduos parentes em primeiro ou segundo graus com ELT, critério adotado por nossa equipe para definição de ELT familiar. Entretanto, estas famílias podem corresponder à uma variação da mesma síndrome. Apenas após a clonagem do(s) gene(s) responsável(is) pela ELTMfamilial e a avaliação molecular de todos os pacientes com ELTM, poderemos saber a real prevalência de casos isolados e familiares.

A determinação do papel de fatores ambientais no fenótipo destes indivíduos somente será possível quando a base genética da ELTMfamilial for devidamente esclarecida. Após determinação do espectro da apresentação clínica e da patologia hipocampal, poderemos então almejar o desenvolvimento de novas terapêuticas específicas para o defeito genético.

CONCLUSÕES

1. Há dois tipos de ELT familial, de acordo com a origem das crises (mesial ou lateral), e assim como os casos não-familiares, a forma mesial é mais freqüente.

2. Na ELTLfamilial, a evolução clínica é benigna e pode haver alterações do desenvolvimento do lobo temporal.

3. Na ELTMfamilial,

a) os indivíduos afetados podem cursar com diferentes graus de severidade, sendo indistintos dos casos não-familiares de ELTM.

b) sinais de EMT na RM são freqüentes, não necessariamente associados a crises refratárias, e podem estar presentes em indivíduos assintomáticos.

c) este fator genético parece não acarretar alterações cerebrais mais difusas.

d) patologia hipocampal mostra padrão clássico de EMT (perda neuronal em CA1, CA3, giro denteado, com preservação de CA2).

e) bom prognóstico cirúrgico quando AH e alterações EEG são unilaterais ou assimétricas.

f) Os heredogramas apresentam padrão de herança autossômica dominante e sugerem um efeito monogênico determinando a patologia hipocampal e levando à síndrome de ELTM; a apresentação fenotípica provavelmente depende da interação com outros fatores modificadores (genéticos e ambientais)

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ANEXOS

Anexo 1

Aprovação do Comitê de Ética em Pesquisa da FCM UNICAMP

UNICAMP

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PARECER PROJETO Nº 166/99

I - IDENTIFICAÇÃO
Título do projeto: EPILEPSIA DE LOBO TEMPORAL FAMILIAR: CARACTERÍSTICAS CLÍNICAS E INVESTIGAÇÃO POR RESSONÂNCIA MAGNÉTICA

Pesquisador responsável: Elcne Kobayashi

V - PARECER DO CEP
O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP, após acatar os pareceres dos membros-relatores previamente designados para o presente caso e atendendo todos os dispositivos das Resoluções 196/96 e 251/97, bem como ter aprovado os termos do Consentimento Livre e Esclarecido, assim como todos os anexos incluídos na Pesquisa, resolve aprovar sem restrições o Protocolo de Pesquisa supracitado.

VI - DATA DA REUNIÃO
A ser homologado na I Reunião Ordinária do CEP em 2000

Prof. Dr. Sebastião Araújo
VICE PRESIDENTE do COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

Anexos 2 e 3

Termo de consentimento para realização de exame de ressonância magnética

FORMULÁRIO DE CONSENTIMENTO PARA PESQUISA MÉDICA, *Página 1 de 3*

Título do projeto: **A Neuroimagem nas Epilepsias**

Investigador principal: Dr. Fernando Cendes

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 para identificar e quantificar alterações estruturais e metabólicas do sistema nervoso central. 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. 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.

FORMULÁRIO DE CONSENTIMENTO PARA PESQUISA MÉDICA, *Página 2 de 3*

Título do projeto: A neuroimagem nas epilepsias parciais.

Investigador principal: Dr. Fernando Cendes

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) 788-8217 estará disponível para responder minhas questões e preocupações. Em caso de recurso, dúvidas ou reclamações contactar a secretaria da Comissão de Ética da Faculdade de Ciências Médicas-UNICAMP, tel. (019) 788-7232.

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.

FORMULÁRIO DE CONSENTIMENTO PARA PESQUISA MÉDICA, *Página 3 de 3*

Título do projeto: A neuroimagem nas epilepsias parciais.

Investigador principal: Dr. Fernando Cendes

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

UNICAMP

Universidade Estadual de Campinas
Departamento de Neurologia

FORMULÁRIO DE CONSENTIMENTO PARA PESQUISA MÉDICA, *Página 1 de 3*

Título do projeto: **Ressonância magnética em indivíduos normais**

Investigador principal: Dr. Fernando Cendes e Dra. Eliane Kobayashi

OBJETIVO DA PESQUISA:

Eu _____ entendo que fui convidado (a) a participar em um projeto de pesquisa envolvendo indivíduos assintomáticos (normais). O objetivo geral do estudo é o de determinar a existência de alterações anatômicas por Ressonância Magnética em pessoas sem qualquer doença neurológica, para comparação com indivíduos epilépticos. A identificação e quantificação dessas anormalidades no cérebro, pode eventualmente melhorar o diagnóstico e levar a um melhor tratamento dessa doença. Além disso, o achado de alterações em indivíduos assintomáticos (que nunca tiveram crises) pode fornecer novas teorias a respeito da origem da epilepsia. 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. O objetivo principal desse estudo é determinar as alterações encontradas em famílias com epilepsia de lobo temporal e m indivíduos afetados e não afetados para estudo de fatores envolvidos na manifestação clínica em cada um desses indivíduos.

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. 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. 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 projeto, e poderão ser úteis no futuro.

FORMULÁRIO DE CONSENTIMENTO PARA PESQUISA MÉDICA, *Página 2 de 3*

Título do projeto: **Ressonância magnética em indivíduos normais**

Investigador principal: Dr. Fernando Cendes e Dra. Eliane Kobayashi

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 ou a Dra. Eliane Kobayashi, tel (019) 788-8217 estarão disponíveis para responder minhas questões e preocupações. Em caso de recurso, dúvidas ou reclamações contactar a secretaria da Comissão de Ética da Faculdade de Ciências Médicas-UNICAMP, tel. (019) 788-7232.

FORMULÁRIO DE CONSENTIMENTO PARA PESQUISA MÉDICA, *Página 3 de 3*

Título do projeto: **Ressonância magnética em indivíduos normais**

Investigador principal: Dr. Fernando Cendes e Dra. Eliane Kobayashi

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. Eu reconheço também que o Dr. Fernando Cendes e a Dra. Eliane Kobayashi podem interromper a minha participação nesse estudo a qualquer momento que julgarem apropriado.

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.

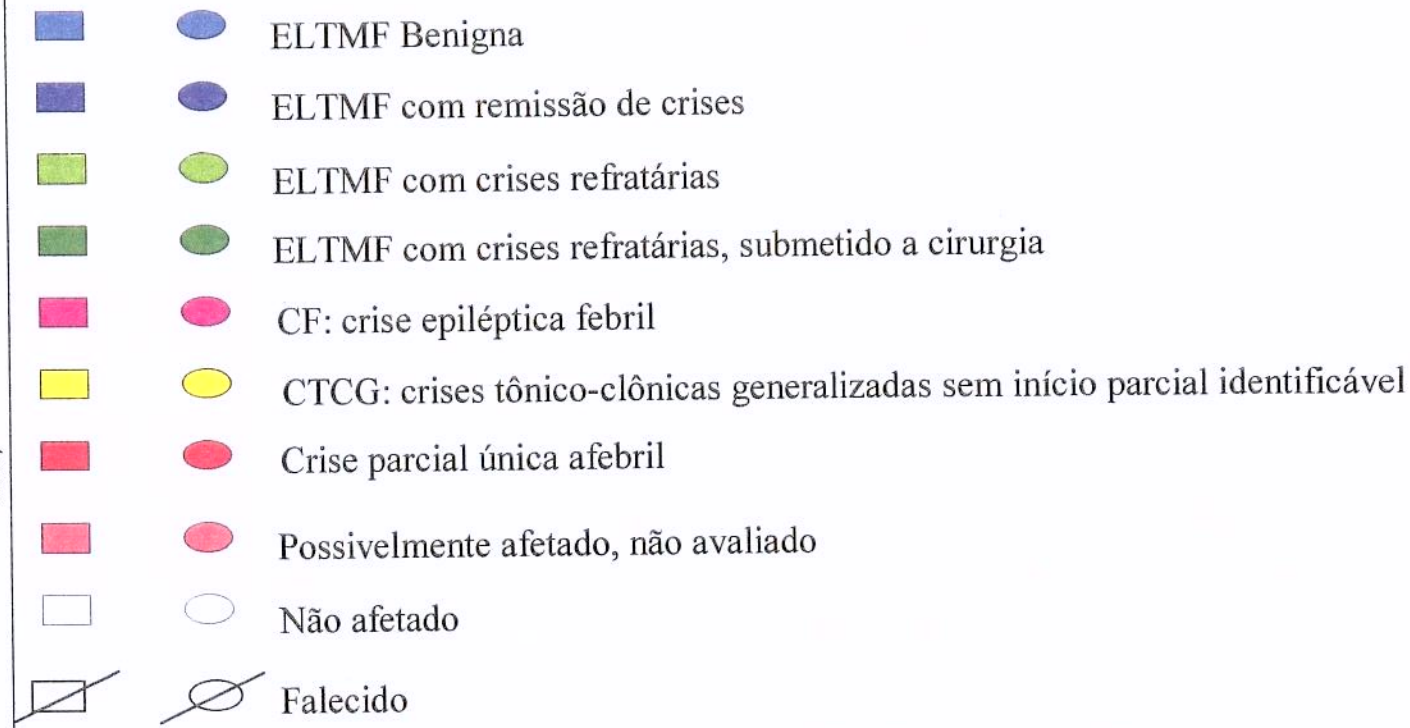
_____
Nome do pesquisador ou associado

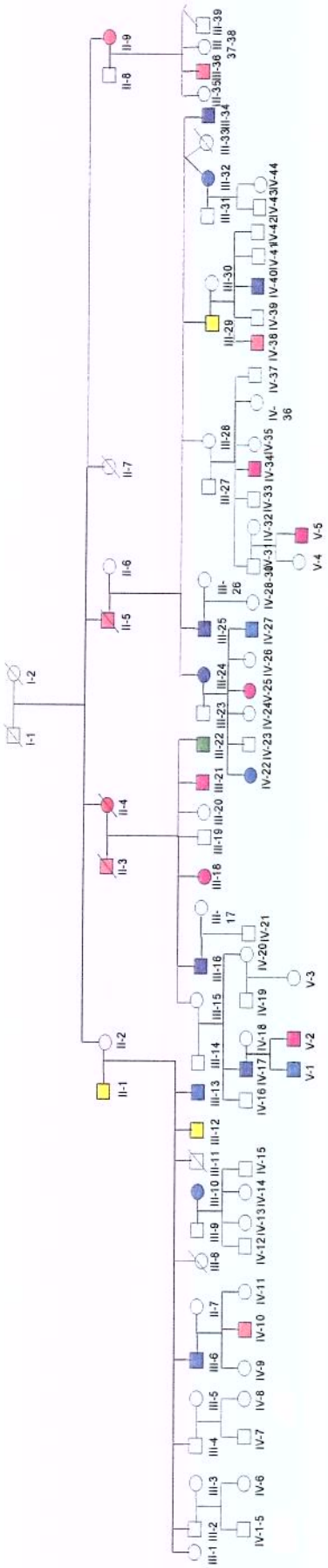
_____ _____
Assinatura do pesquisador ou associado data

Anexo 4

Heredogramas

Legenda para heredogramas:

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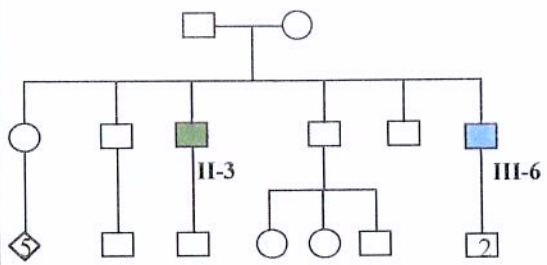
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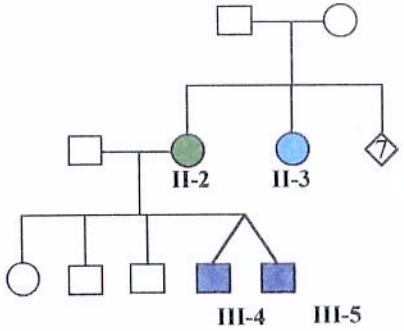
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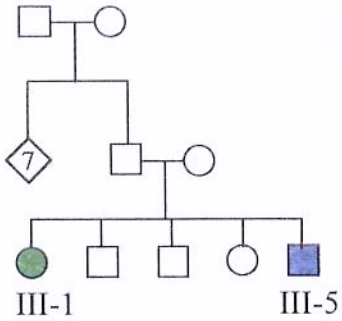
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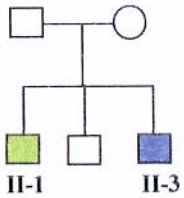
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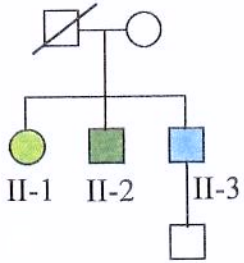
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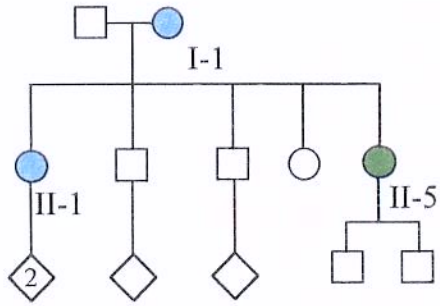
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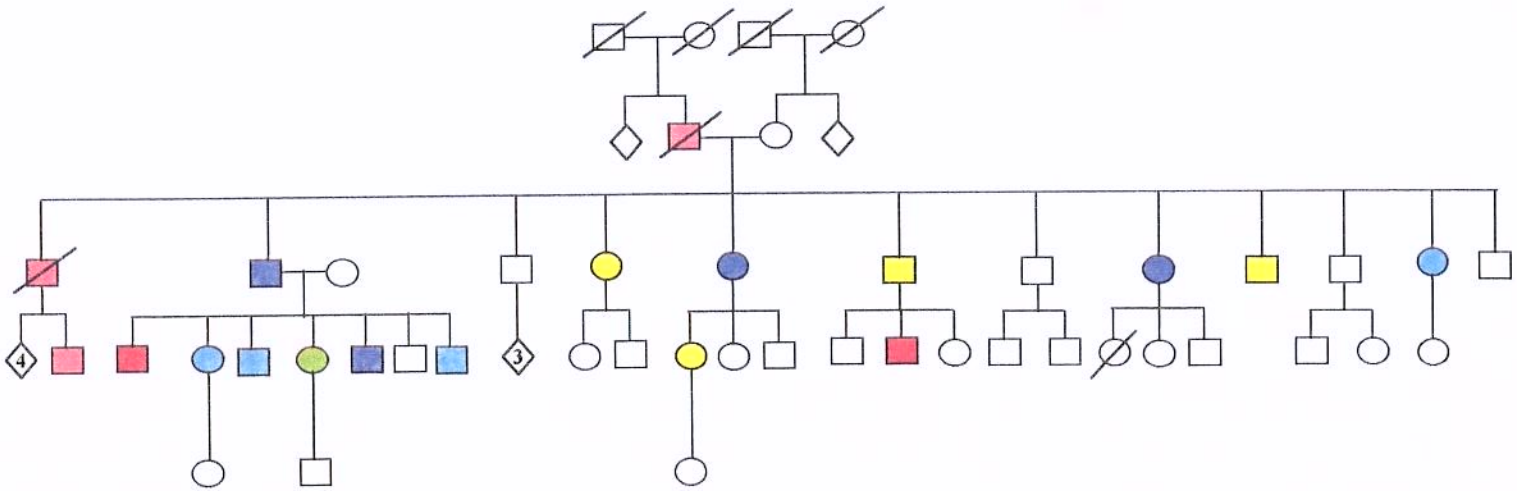
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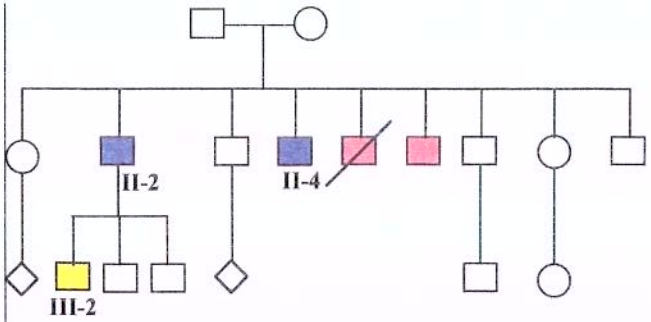
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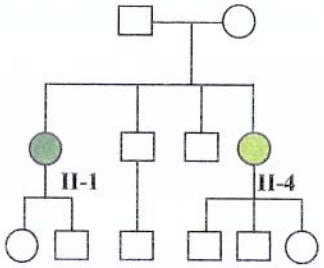
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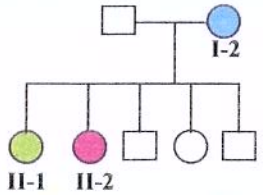
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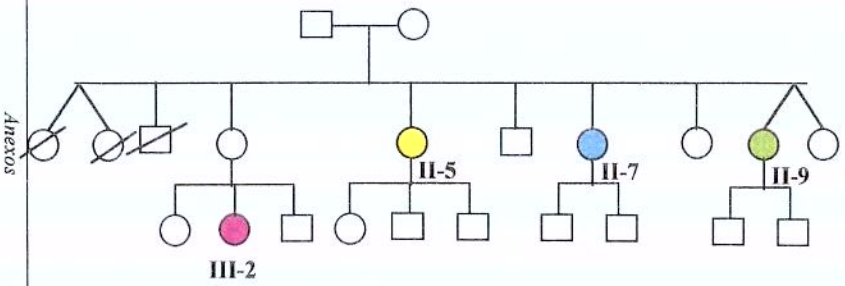
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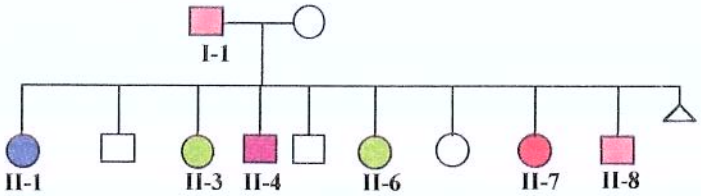
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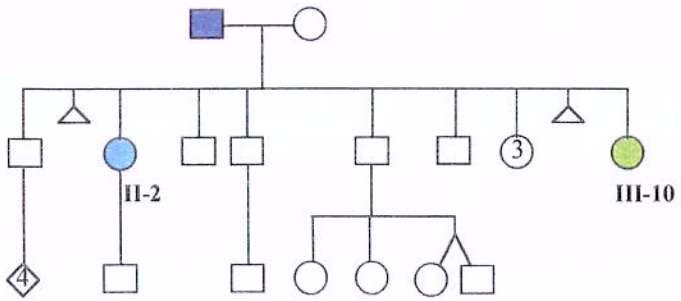
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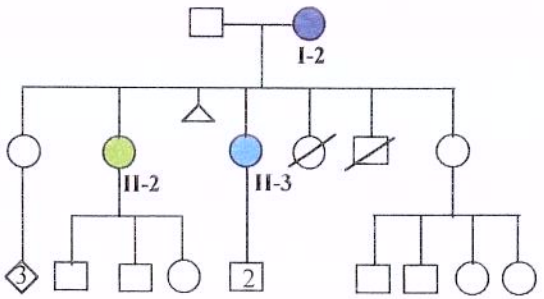
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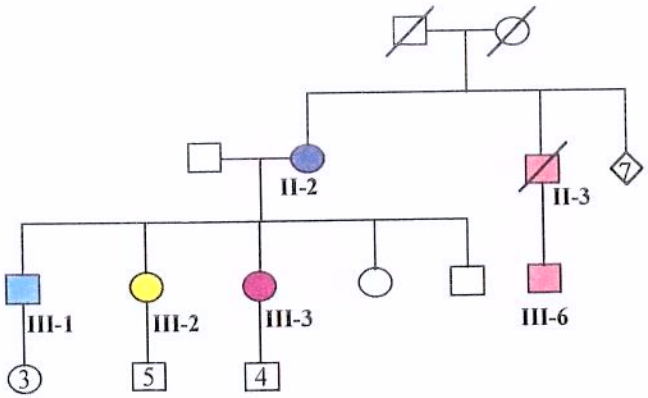
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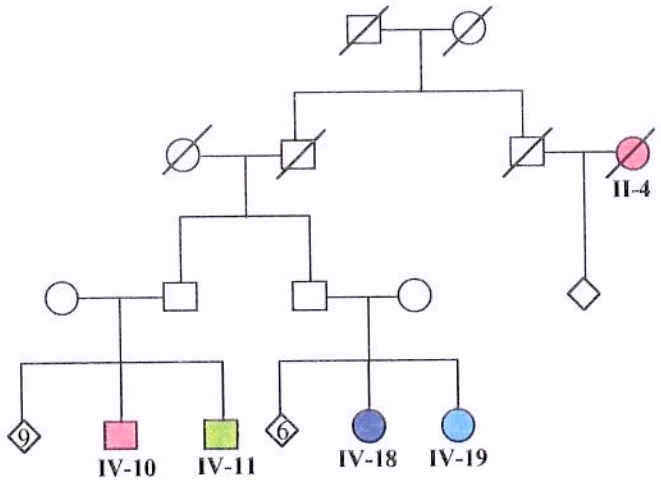
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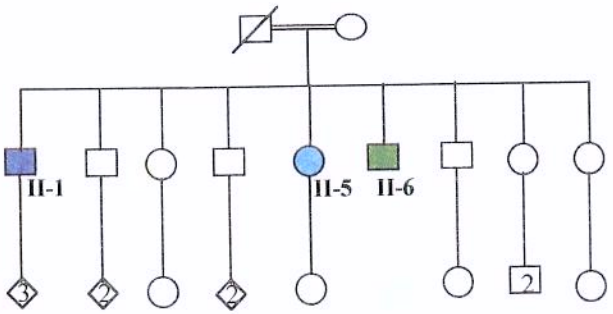
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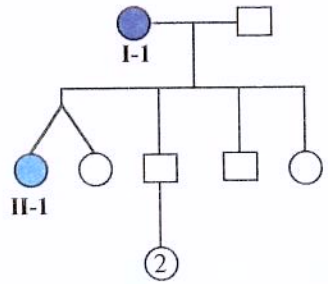
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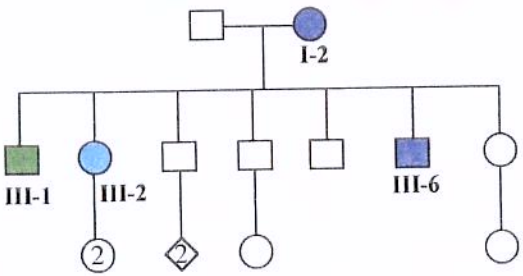
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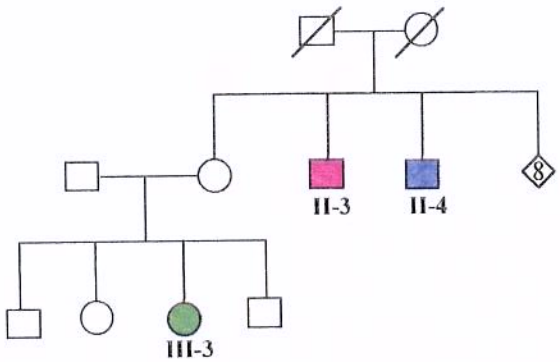
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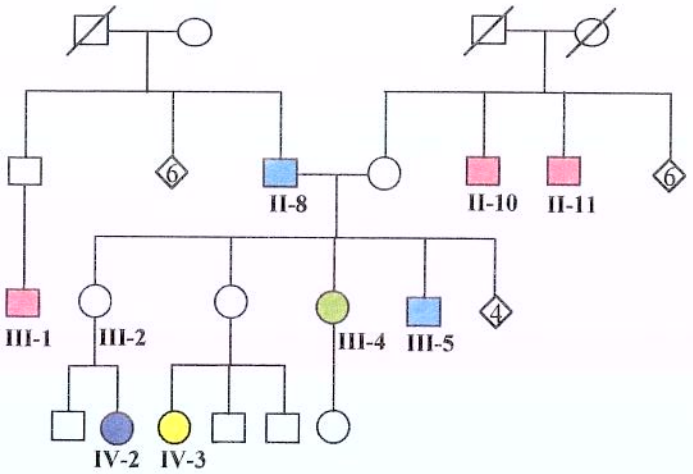
III-3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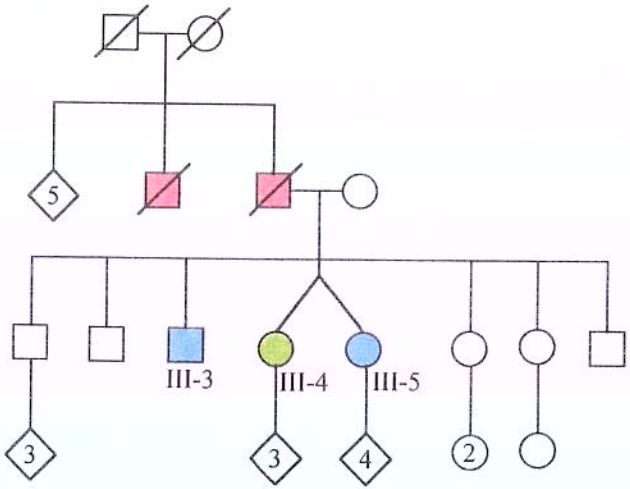
IV-2
IV-3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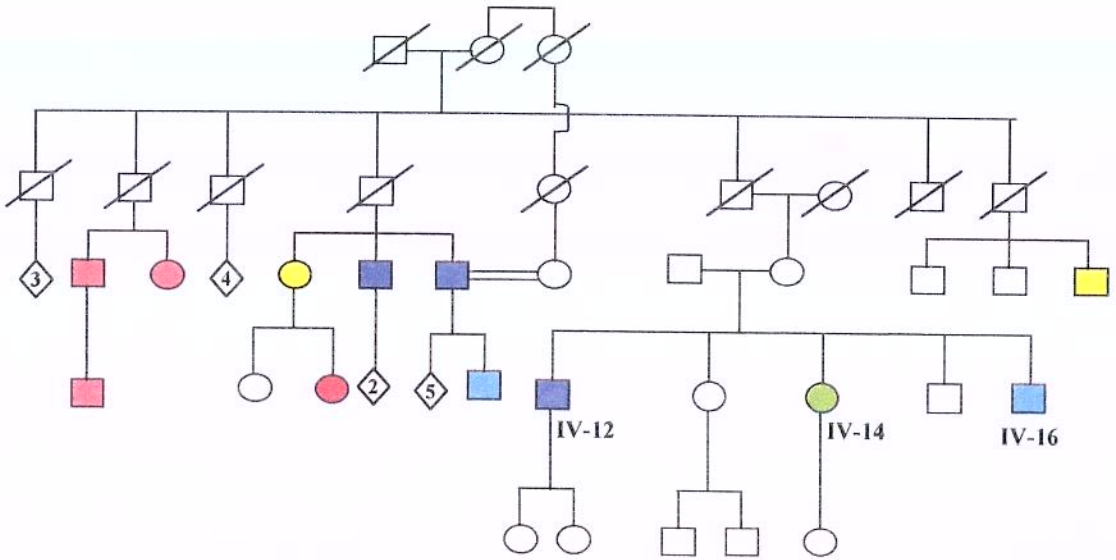
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IV-14
IV-16