PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA

MARTA HEMB

RELAÇÃO ENTRE INJÚRIA PRECIPITANTE INICIAL E DANO HIPOCAMPAL NA DISPLASIA CORTICAL FOCAL TIPO I

Porto Alegre
2010

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RESUMO

Introdução: As displasias corticais focais (DCF) são o substrato etiológico mais comum na cirurgia da epilepsia pediátrica. Pacientes com DCF tipo I frequentemente apresentam esclerose hipocampal (EH), porém os mecanismos subjacentes à lesão hipocampal em tais pacientes são desconhecidos. Realizamos um estudo clínico-patológico para identificar os mecanismos patogênicos da lesão hipocampal em crianças com epilepsia do lobo temporal (ELT) refratária associada à DCF.

Métodos: Foram incluídos pacientes com epilepsia refratária operados no lobo temporal (LT) cujo exame neuropatológico revelou DCF (grupos DCF tipo I e II). Como grupos de comparação, foram incluídos pacientes com tumores de baixo grau (grupo TBG), pacientes com ELT sem lesões neocorticais com ou sem esclerose hipocampal (grupo EH/SLN) e controles de autópsia (grupo Autópsia). As variáveis clínicas foram correlacionadas com a presença de danos no hipocampo (avaliados através de ressonância magnética, exame histopatológico e densidades neuronais).

Resultados: Um total de 108 crianças foi incluído no estudo: 41 pacientes no grupo EH/SLN (38%), 32 pacientes no grupo DCF tipo I (29,6%), 20 pacientes no grupo TBG (18,5%), 5 pacientes no grupo DCF tipo II (4,6%) e 10 casos de necrópsia (9,3%). A prevalência de uma injúria precipitante inicial (IPI) foi pequena no grupo TBG, intermediária nos grupos DCF tipos I e II e alta no grupo EH/SLN ($P < 0,001$). Quando comparados ao grupo Autópsia, metade dos pacientes do grupo DCF tipo I apresentou danos hipocampais. A análise mostrou que, nos grupos DCF tipo I e EH/SLN, a presença de um IPI foi associada a uma menor densidade neuronal na fascia dentada (FD) e setor de Sommer [CA1 e prosubiculo (PRO)].

Conclusão: Nossos resultados suportam a visão de que, semelhante aos pacientes com epilepsia do lobo temporal associada a esclerose hipocampal (ELTM-EH), o mecanismo de lesão hipocampal em pacientes com DCF tipo I parece estar relacionado a um IPI.

Unitermos: displasia cortical focal, esclerose hipocampal, epilepsia pediátrica, injúria precipitante inicial.

ABSTRACT

Background: Focal cortical dysplasias (FCD) are the most common etiological substrate in pediatric epilepsy surgery. Type I FCD patients frequently have hippocampal sclerosis (HS) but the mechanisms underlying hippocampal damage in such patients is unknown. We performed a clinical-pathological study to identify the pathogenic mechanisms of hippocampal damage in children with refractory temporal lobe epilepsy (TLE) associated with FCD.

Methods: We included patients with refractory epilepsy operated on the temporal lobe (LT) whose neuropathological examination revealed FCD (FCD type I and II groups). As comparison groups, we included patients with temporal low-grade tumors (LGT group), patients with TLE without neocortical lesions with or without hippocampal sclerosis (HS/NNL group), and autopsy controls (Autopsy group). Clinical variables were correlated with the presence of hippocampal damage evaluated by MRI, histopathology and neuronal densities.

Results: A total of 108 children were included in the study, 41 patients in the HS/NNL group (38%), 32 in FCD type I group (29.6%), 20 patients in LGT group (18.5%), 5 patients in FCD type II group (4.6%), and 10 autopsy cases (9.3%). The prevalence of an initial precipitating injury (IPI) was low in LGT group, intermediate in FCD type I and II groups, and high in HS/NNL group (P<0.001). Half patients in the FCD type I group had hippocampal damage in qualitative studies and lower neuron densities in several hippocampal subfields when compared with Autopsy group. The analysis showed that in FCD type I and HS/NNL groups the presence of an IPI was associated with lower neuronal densities in fascia dentate (FD) and Sommer's sector [CA1 and prosubiculum (PRO)].

Conclusion: Our results support the view that, similar to mesial temporal lobe epilepsy associated HS (MTLE-HS) patients, the mechanism of hippocampal damage frequently seen in type I FCD patients appears to be related to an IPI.

Keywords: Focal cortical dysplasia, hippocampal sclerosis, pediatric epilepsy, initial precipitating injury, dual pathology.

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LISTA DE SIGLAS

FMRP-USP	Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo
ILAE	*International League Against Epilepsy*
UCLA	Universidade da Califórnia, Los Angeles

LISTA DE ABREVIATURAS

CA	Corno de Ammon
CE	Córtex entorrinal
CPC	Crises parciais complexas
CPS	Crises parciais simples
DCF	Displasias corticais focais
DP	Desvio padrão
EEG	Eletroencefalograma
EH	Esclerose hipocampal
EH/SLN	Esclerose hipocampal com ou sem lesão neocortical
ELT	Epilepsia do lobo temporal
ELTM	Epilepsia do lobo temporal mesial
ELTM-EH	Epilepsia do lobo temporal mesial associada à esclerose hipocampal
ELTN	Epilepsia do lobo temporal neocortical
FAEs	Fármacos antiepilépticos
FD	Fascia dentada
FDG-PET	^{18}F-flúor-deoxi-2-glicose *positron emission tomography*
FDI	Fascia dentada inferior
FDS	Fascia dentada superior
GD	Giro denteado
HE	Hematoxilina- eosina
IPI	Injúria precipitante inicial
LT	Lobo temporal
MDC	Malformação do desenvolvimento cortical
mMCD	Malformações leves do desenvolvimento cortical
PRO	Prosubiculo
RM	Ressonância magnética
SE	*Status Epilepticus*

SEM	Desvio padrão da media
SNC	Sistema nervoso central
SPECT	*Single photon emission computed tomography*
SUB	Subículo
TBG	Tumores de baixo grau
TCE	Traumatismo cranioencefálico

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1 INTRODUÇÃO

1.1 A EPILEPSIA

A palavra epilepsia é derivada do verbo grego *epilamvanein*, que significa "ser atacado", "ser convulsionado". Esta terminologia vem de antigas idéias de que todas as doenças representavam ataques dos deuses ou dos maus espíritos, como uma forma de castigo. Pelo fato das crises convulsivas terem sido o exemplo mais vívido da possessão do demônio, a epilepsia era considerada uma doença sagrada e, apenas ao final do século V DC, a palavra foi gradualmente adquirindo o significado que tem hoje. [1]

A epilepsia pode ser definida como um transtorno intermitente do sistema nervoso central (SNC) devido a uma descarga excessiva e desordenada do tecido cerebral. Esta descarga pode resultar em perda da consciência, em alteração da percepção ou em prejuízo da função psíquica; assim como em movimentos convulsivos, distúrbios das sensações, ou alguma combinação destes. [2]

A epilepsia não é uma doença específica ou uma síndrome única, mas sim uma junção de sintomas complexos provenientes de alguma alteração da função cerebral que pode ser secundária a uma variedade de processos patológicos. As epilepsias são divididas em desordens idiopáticas e sintomáticas. Quando idiopáticas, geralmente são benignas, não estando relacionadas a lesões cerebrais, anormalidades neurológicas (exceto crises convulsivas) ou prejuízo mental e tendem a ser auto-limitadas ou responderem prontamente aos fármacos antiepilépticos (FAEs). Quando sintomáticas, são consequentes a uma lesão identificada ou a uma etiologia específica. Quando a epilepsia é presumidamente sintomática, porém de etiologia não conhecida, é chamada de provavelmente sintomática ou criptogênica. [3]

Na prática da neurologia pediátrica, a epilepsia é uma das doenças mais comuns. A maioria das epilepsias inicia-se na infância, sendo a diversidade de apresentações muito grande nesta faixa etária.

1.1.1 A Epilepsia do Lobo Temporal e a Esclerose Hipocampal

A epilepsia do lobo temporal (ELT) foi definida pela *International League Against Epilepsy* (ILAE) como uma condição caracterizada por crises recorrentes não provocadas originárias das porções mesiais ou laterais do lobo temporal (LT).

A ELT é a forma mais comum de epilepsia focal nos adultos (40% dos casos) e também o tipo mais freqüente de epilepsia refratária nesta população, compreendendo 75% dos pacientes operados. [4-7]

As crises associadas à ELT podem ser parciais simples (CPS), sem perda de consciência; ou parciais complexas (CPC), com perda de consciência podendo, secundariamente, generalizarem-se. De acordo com a localização anatômica do início das crises, as ELTs podem ser classificadas em ELT mesial (ELTM), quando as crises iniciam no hipocampo, uncus ou amígdala; ou ELT neocortical (ELTN), quando as crises originam-se das superfícies laterais e inferiores do LT. [8]

Dentre suas etiologias mais comuns incluem-se a esclerose hipocampal (EH), os tumores de baixo grau (TBG), as displasias corticais focais (DCF) e as lesões vasculares, entre outras. A EH é a alteração patológica mais encontrada em adultos jovens com epilepsia focal refratária, compreendendo 50-70% dos casos e não sendo tão comum nas séries pediátricas. [9, 10] O fato de a EH apresentar uma aparente baixa prevalência durante a infância, assim como o fato de ser uma patologia freqüentemente associada a crises febris complicadas no início da vida, sugere que possa ser parte de uma doença progressiva, caracterizada por apresentar uma primeira lesão precoce, seguida de um período latente de longa duração até o desenvolvimento de uma epilepsia crônica refratária. [11, 12]

A semiologia da ELT em adultos inclui auras típicas, como uma sensação epigástrica ascendente, sensação de medo, sensação de *déjà vu* ou *jamais vu*, assim como alucinações olfativas e gustativas. [13-15] A aura pode ser seguida por uma parada motora e comportamental, diminuição da capacidade de resposta e alteração da consciência. Crises autonômicas como piloereção, palpitação e dilatação pupilar, também podem ocorrer. Automatismos oroalimentares e de extremidades distais superiores são características comuns das ELTs, assim como

uma distonia contralateral, reconhecida como um importante sinal de lateralização. [16] Algum grau de disfunção cognitiva e de linguagem pós-ictal pode estar presente nos pacientes com crises mesiais, sendo a intensidade das disfunções dependentes do envolvimento do hemisfério dominante. [17]

Nas crianças, em que a ELT é, na maioria das vezes, secundária a etiologias que não EH, como TBG e malformações do desenvolvimento cortical (MDC), a semiologia das crises é diferente. Lactentes apresentam proeminentemente, manifestações motoras, o que se torna menos evidente com o aumento da idade. Apesar de automatismos também serem vistos em crianças com ELT, estes são mais simples e menos elaborados. É importante lembrar que crianças com epilepsia parcial podem apresentar manifestações iniciais de natureza generalizada como espasmos infantis, o que pode ter profundas implicações em suas avaliações pré-cirúrgicas. [13, 18]

O eletroencefalograma (EEG) de escalpo interictal pode demonstrar anormalidades não epileptiformes caracterizadas por um alentecimento basal intermitente nas faixas teta e delta. Descargas temporais mesiais tipo ponta e ponta-onda agudas unilaterais ou bilaterais independentes, também podem ocorrer. Contudo, alguns pacientes apresentam EEG interictal normal, o que não exclui o diagnóstico de ELTM. [19] No EEG ictal, uma atividade epileptiforme do tipo ponta e onda aguda, seguida ou não de onda lenta, é registrada com eletronegatividade máxima nos eletrodos T3-F7/T4-F8 e especialmente nos eletrodos esfenoidais. Um dos padrões ictais típicos é o de uma atividade rítmica na faixa de 5 a 7 HZ, vista no início da CPC e presente em até 80% dos casos. [17, 19, 20]

O diagnóstico de ELTM através da ressonância magnética (RM) traduz-se por uma diminuição do volume ou aumento do sinal hipocampal nas sequências ponderadas em T2 ou FLAIR, podendo ser acompanhados de modificação no formato e na estrutura interna do mesmo. A atrofia do hipocampo pode ser unilateral ou bilateral e mais comumente é assimétrica e vista em T1. [21-24]

O FDG-PET, nos casos de epilepsia do lobo temporal mesial associada à esclerose hipocampal (ELTM-EH), frequentemente mostra um hipometabolismo que compreende regiões além do hipocampo, como todo o LT, tálamo, núcleos da base

e outras áreas neocorticais. [25-27] Esta observação suporta a visão de que a ELTM envolve mecanismos diferentes das outras epilepsias neocorticais que mostram pouca ou nenhuma área de hipometabolismo, que não a área da lesão estrutural em si. [28]

O SPECT é característico: quando ictal mostra hiperperfusão temporal unilateral e, quando pós-ictal, hipoperfusão temporal lateral com hiperperfusão medial. [29] Em relação ao SPECT interictal, sua precisão é de cerca de 70%, considerada baixa. Todavia, a acurácia do SPECT ictal na ELT é de cerca de 90%, considerada alta e semelhante à do FDG-PET. [30]

1.1.1.1 A Histopatologia da Esclerose Hipocampal e o Dano Hipocampal Progressivo

O termo formação hipocampal refere-se a uma unidade funcional complexa, encontrada na porção mesial do LT, constituída pelo hipocampo ou corno de Ammon (CA), subículo (SUB), giro denteado (GD) e córtex entorrinal (CE). [31] Microscopicamente, o hipocampo possui quatro zonas distintas (CA1, CA2, CA3 e CA4) distribuídas a partir do SUB em direção ao GD. Cada uma dessas regiões mantém um padrão organizado de conexões intrínsecas e extrínsecas. As fibras que deixam o CE em direção ao hipocampo constituem a via perfurante e inervam as células granulares do GD. Os axônios das células granulares (fibras musgosas) projetam-se para as células piramidais da região de CA3, que por sua vez emitem fibras para a região de CA1, constituindo a chamada via colateral de Schaffer. A partir de CA1, as fibras projetam-se para o SUB e então para as camadas profundas do CE.

Considerando a sensibilidade à hipóxia, o setor CA1, também chamado setor de Sommer, é denominado setor vulnerável; CA2 e CA3, em conjunto, são chamados setor de Spielmeyer, ou setor resistente; e CA4, adjacente ao GD, é o setor de Bratz ou setor de vulnerabilidade média. [32]

O hipocampo de pacientes com ELTM-EH apresenta um padrão

estereotipado de lesão, caracterizado por uma perda neuronal severa e gliose no setor de Sommer [CA1 e prosubiculo (PRO)] e no endofolio (hilo e CA4), assim como uma perda celular menos severa na FD, sendo que o SUB e o córtex transicional também podem apresentar perda neuronal sutil. [8, 9] As crianças com ELT apresentam perdas neuronais em quantidade e padrão similares aos adultos: maiores perdas em CA1, PRO, hilo e CA4, com relativa preservação das células de CA3 e CA2. [8]

Nas últimas décadas, ficou claro que nas doenças em que existe excessiva atividade neuronal, como na ELT, pode existir um remodelamento celular secundariamente induzido por crises. Uma perda neuronal seletiva, assim como alterações da organização interna do GD, particularmente a dispersão das células granulares e a reorganização axonal, constituem achados frequentemente associados à EH. [33, 34] A perda celular hipocampal está intimamente relacionada à reorganização axonal no GD. As fibras musgosas que normalmente inervam as células piramidais de CA3 e as células do hilo, na EH, projetam-se para a camada molecular interna do GD, estabelecendo um circuito recorrente com as células granulares. Vários estudos têm sugerido que o brotamento axonal (*sprouting*) destas fibras musgosas constitui um substrato para a gênese das crises em humanos e modelos experimentais. [35-38] Recentemente, foram observados neurônios megálicos com arborização dendrítica anômala (neurônios dismórficos), semelhantes àqueles observados nas DCFs, no GD de hipocampos escleróticos. [39] Outros trabalhos também mostram que a frequência de crises generalizadas, assim como a duração da epilepsia, está diretamente relacionada à progressão da perda neuronal hipocampal e consequente atrofia do mesmo. [11, 40-42]

1.1.2 A Injúria Precipitante Inicial

Injúria precipitante inicial (IPI) compreende qualquer evento médico que apresente implicações neurológicas secundárias ao mesmo. [43] A ELTM-EH está frequentemente associada a um IPI ocorrido durante a infância. [11, 44, 45] Atualmente, sabe-se que são os pacientes com história de uma crise sintomática inicial

associada a um trauma ao nascimento, traumatismo cranioencefálico (TCE), *status epilepticus* (SE), infecção do SNC ou crises febris, que parecem compreender o grupo de risco para desenvolvimento de epilepsia. [44] French e colaboradores relataram que de sessenta pacientes estudados com ELT, aproximadamente todos apresentavam uma historia de IPI, sendo IPI tipo crise febril encontrado em 53% dos casos. [46]

Meyer já especulava estar a EH associada a uma história prévia de IPI, sendo a ELTM provavelmente o resultado de algum evento ocorrido no passado, e não consequência de crises repetidas. [45] Mathern e colaboradores, "revisitando a hipótese de Meyer", através de uma revisão de quinhentos e setenta e dois pacientes com ELT, observaram uma associação entre IPI e EH em 87% dos casos avaliados. Os autores constataram uma diminuição na densidade neuronal hipocampal naqueles com uma longa história de epilepsia e enfatizaram que este tipo de perda neuronal só era vista em pacientes com mais de trinta anos de doença, e que a mesma era difusa e não restrita a subcampos específicos. Concluíram que crises mesiais ocorrendo por longas décadas contribuem para a redução da população neuronal e atribuíram ao IPI o papel de promover dano neuronal capaz de produzir as condições necessárias para gerar crises epilépticas espontâneas. [11] Já em outro estudo, estes mesmos autores ressaltam que o tipo de IPI, assim como a idade em que o mesmo ocorre, pode determinar o substrato patológico que irá, eventualmente, levar a uma ELTM intratável. Sendo assim, a lesão hipocampal resultante de um IPI pode não ser necessariamente uma lesão estática com transformação imediata em área epileptogênica. É possível que o hipocampo lesado modifique-se progressivamente ao longo do tempo, visto que, na maioria dos pacientes, observa-se um período silencioso entre o IPI e o início das crises. [44]

Pesquisas em neuroimagem apontam uma associação entre EH e anomalias do desenvolvimento do hipocampo, sugerindo que um dano hipocampal preexistente possa levar a crises febris e ELT secundária. Um estudo de RM foi realizado após crises febris complexas em vinte e sete crianças. Anormalidades hipocampais preexistentes foram encontradas em diversas destas crianças, sugerindo a possibilidade de que as crises febris realmente originar-se-iam nos LTs em alguns pacientes. [47]

1.1.3 A Hipótese do Segundo Insulto

A hipótese do segundo insulto afirma existir um insulto inicial que leve a uma diminuição do limiar convulsivo e, posteriormente, um segundo insulto que resulte na expressão da epilepsia. Pressupõe que crises no cérebro imaturo resultem em alterações que tornam o cérebro maduro mais suscetível a subsequente injúria induzida por crises. [42] Alguns dados experimentais reforçam essa hipótese. Koh e colaboradores mostraram que em ratos, apesar de um SE no décimo quinto dia de vida não resultar em uma lesão detectável ou morte celular cerebral, predispõe os animais a lesões neuronais mais extensas após um segundo insulto. Apesar de o uso de ácido caínico, como indutor de crises convulsivas, não causar prejuízo no aprendizado espacial, ratos que sofreram crises precoces quando na idade adulta, apresentam pior desempenho do que aqueles que sofreram crises apenas quando já mais velhos, o que sugere que crises precoces predispõem o SNC ao efeito danoso de crises tardias. [48]

Nas epilepsias parciais, a maioria das evidências aponta em direção a um paradigma de epileptogênese, em que as crises são as expressões clínicas de um processo patogênico. Este paradigma seria iniciado por um evento que ativaria moduladores críticos que, por sua vez, ao longo de meses ou anos produziriam alterações estruturais e funcionais cerebrais. Tais alterações poderiam ser expressas como crises não provocadas recorrentes em indivíduos suscetíveis, particularmente se o indivíduo fosse exposto a outro insulto neurológico - o segundo insulto - que desencadearia a expressão clínica da epilepsia. As crises agiriam como substrato epileptogênico causando alterações estruturais e funcionais adicionais. [49, 50]

Em relação à ELT, a hipótese do segundo insulto sugere que existam dois fatores envolvidos na sua etiologia: 1) IPI somado a 2) outro fator que aumente a vulnerabilidade do indivíduo a uma injúria hipocampal. [51] Dentre estes fatores que ajudariam a explicar o aumento da vulnerabilidade do hipocampo a uma injúria e subseqüente desenvolvimento de EH estão: as disgenesias, incluindo as DCFs; a predisposição genética; e as crises febris prévias, apesar de sabermos que a maioria

das crianças que apresenta crises febris nunca desenvolve EH ou ELT. [51, 52]

1.2 A DISPLASIA CORTICAL FOCAL

As MDCs são reconhecidas como uma das mais importantes causas de epilepsia em crianças e adultos. [53, 54] Foi em 1996, que Barkovich sugeriu o termo MDC pelo fato de que, como um grupo, estas malformações serem o resultado de uma organogênese cortical alterada. [55] Este mesmo autor propôs um sistema de classificação das MDCs, ainda hoje usado, baseado nas três etapas principais do desenvolvimento cortical: 1) proliferação e diferenciação celular; 2) migração neuronal; e 3) organização cortical, sendo que, interferências em quaisquer destas etapas seriam capazes de resultar em diferentes tipos de MDCs. Entre as malformações focais devidas à proliferação neuronal e glial anormal,encontramos uns dos mais comuns subtipos de MDCs, as DCFs, responsáveis por grande parte dos casos de epilepsia parcial refratária ao tratamento medicamentoso. [56]

As DCFs compreendem o substrato etiológico mais comum na cirurgia da epilepsia de crianças perfazendo, aproximadamente, 40% dos casos, e um dos mais comuns em adultos. [57-60] As DCFs podem ocorrer isoladamente em um lobo ou em múltiplos lobos ao mesmo tempo, assim como podem apresentar vários tamanhos e localizações. [61] As DCFs podem ocorrer em combinação com uma segunda patologia cerebral principal, como EH, TBGs, malformações vasculares, cicatrizes perinatais ou infartos.

De acordo com o esquema de classificação mais utilizado, as DCFs podem ser divididas em: leve, tipo I; e severa tipo II, além das malformações leves do desenvolvimento cortical (*mMCD*). O tipo I é caracterizado exclusivamente por desorganização e deslaminação cortical (DCF tipo IA), ou pode também incluir neurônios piramidais hipertróficos fora da camada V (DCF tipo IB). Além dos distúrbios da laminação da arquitetura cortical vistos no tipo I, as DCF tipo II apresentam alterações histopatológicas importantes, incluindo neurônios dismórficos (DCF tipo IIA) ou células em balão (DCF tipo IIB). Já as *mMCD*s, são caracterizadas

por apresentarem um córtex normal com a presença de neurônios em excesso na camada I ou substância branca subcortical. [62]

A semiologia das crises depende basicamente da localização da displasia, sendo vista, especialmente, atividade clônica parcial nas crises originárias do LT. Se provenientes do lobo frontal, a maioria das crises compreende uma postura tônica e quando provenientes do lobo occipital, compreendem movimentos oculares. As crises podem apresentar generalização secundária e, em aproximadamente 50% dos pacientes, os espasmos infantis são a manifestação inicial. [63, 64]

O EEG de escalpo de pacientes com DCF não mostra nenhum padrão interictal ou ictal que seja exclusivamente associado a esta patologia e, frequentemente, não é localizatório. [65] No entanto, a presença de descargas epileptiformes focais e rítmicas mostrando correlação espacial com a área displásica, parece ser o padrão eletroencefalográfico ictal mais característico dos pacientes com DCFs. [66] Dados recentes indicam que não existem resultados eletroencefalográficos consistentes que diferenciem pacientes com DCF tipo I dos pacientes com tipo II. [61, 65, 67]

Quanto à RM, sabemos que existem várias características capazes de identificar áreas de DCFs em pacientes com epilepsia refratária. [68-74] São elas: 1) aumento da espessura da substância cinzenta, muitas vezes com padrões girais anormais; 2) borramento da junção da substância branco-cinzenta; 3) aumento de sinal em T2 e FLAIR na substância branca subcortical e cinzenta; e 4) alterações na sustância branca que podem estender-se do córtex ao ventrículo, denominadas sinal *transmantle.* [75] É importante ressaltar que no cérebro imaturo é difícil identificar o aumento de sinal em T2 e o borramento da junção substância branco-cinzenta é um sinal normal no período de maturação cerebral pós-natal. [76] A RM pode ser relatada como normal ou não específica para o diagnóstico de DCF em uma proporção substancial de pacientes com posterior diagnóstico confirmado por histopatologia. [65, 77-81] Em estudos atuais, estas características de imagem foram mais frequentemente associadas à DCF tipo II, em comparação a pacientes com DCF tipo I. [61, 65]

O FDG-PET tem se mostrado uma das técnicas mais sensíveis na identificação de áreas de DCF e muitos pacientes com RM normal apresentam FDG-

PET positivos, mostrando sua importância na complementação da avaliação pré-operatória. [82-84]

O SPECT ictal é outra ferramenta de neuroimagem que tem sido aplicada em pacientes quando existem dúvidas diagnósticas quanto a uma provável DCF, e assim como acontece com o FDG-PET, mais da metade dos pacientes com RM normal apresentam SPECT ictal localizatório. [65, 78, 85]

Apesar de pertencerem à mesma categoria patológica, os pacientes com DCFs tipo I e II apresentam perfis clínicos distintos. Os pacientes com DCF tipo I apresentam uma doença mais difusa, um dano cognitivo mais severo, e um pior controle das crises convulsivas no pós-operatório. [61, 67] Já os pacientes com DCF tipo II, são mais jovens no início das crises, mais jovens na cirurgia, e apresentam maior frequência de crises. [65]

Diferentes mecanismos patogênicos podem estar implicados na formação dos dois tipos de DCFs. O tipo I parece ser secundário a uma organização cortical anormal adquirida em estágios avançados do desenvolvimento cortical, após término da maior parte do período de proliferação celular. O tipo II, caracterizado histologicamente pela presença de células que, em estágios precoces do desenvolvimento falharam em diferenciar-se, seria provavelmente, secundário a uma proliferação celular anormal. [58, 59] Suportando esta teoria, os pacientes com DCF tipo I apresentam mais frequentemente ELT assim como história de problemas perinatais e estão mais associados à EH, uma patologia provavelmente adquirida. [61, 86]

1.3 A DUPLA PATOLOGIA

A presença de dois ou mais substratos epileptogênicos em pacientes com epilepsia refratária não é um achado incomum. A chamada dupla patologia usualmente refere-se à presença de EH somada a uma segunda patologia cerebral epileptogênica principal, identificada por neuroimagem ou por microscopia. [87] Um tecido displásico, micro ou macroscópico, é frequentemente observado em associação com EH em espécimes cirúrgicas de pacientes com ELTM, estimando-se

que uma dupla patologia ocorra em 5-30% dos casos de ELT. [88-90] Em um trabalho muito recente viu-se que dos duzentos e quarenta e três pacientes cirurgicamente tratados para ELT, 117 (48%) apresentaram EH e uma dupla patologia foi encontrada em 83 (71%) casos. A associação EH-tumor compreendeu apenas 6 dos 110 pacientes (7%), enquanto que a associação EH- MDC foi vista em 77 (70%), sendo que em 83% dos casos o tipo de MDC encontrada foi a DCF tipo I. [91]

1.3.1 Os Mecanismos do Dano Hipocampal em Pacientes com DCF

A existência de uma dupla patologia no LT tem sido cada vez mais vista e evidências sugerem que envolva um mecanismo patogênico comum iniciado durante a embriogênese ou desenvolvimento cerebral precoce. Em uma série de pacientes de Montreal, aqueles que apresentavam uma lesão na RM foram avaliados quanto à volumetria hipocampal. Atrofia do hipocampo estava presente em 15% daqueles que apresentavam outras lesões estruturais no LT. Os autores encontraram dano hipocampal mais importante nas imagens dos pacientes com desordem da migração neuronal e cistos porencefálicos do que naqueles com tumores, o que sugere que a dupla patologia seja mais frequente em pacientes em que a lesão ocorreu em uma fase precoce da vida, quando o hipocampo está mais vulnerável ao dano excitotóxico, do que em lesões associadas à ELT que iniciam em uma idade mais tardia. [90] Estudos moleculares neuropatológicos com foco nos aspectos do desenvolvimento da organização hipocampal também indicam que a EH possa ser uma desordem resultante de alterações no desenvolvimento. [34] Por outro lado, Thom e colaboradores identificaram esclerose do LT em 11% dos seus pacientes cirurgicamente tratados. Em relação aos achados neuropatológicos, sugeriram que as características principais eram representadas por áreas de perda neuronal nas camadas supragranulares, indicando que este aspecto possa representar um processo adquirido. [92] Uma explicação alternativa para coexistência de DCF e EH seria o desenvolvimento secundário de EH a partir das crises induzidas por DCF ou crises resultantes do efeito combinado de EH e DCF. [87]

De fato, os mecanismos patogênicos da perda neuronal hipocampal

permanecem desconhecidos. [71] Em adultos, tem-se sugerido que a proximidade da lesão com as estruturas mesiais do LT através de um mecanismo tipo *kindling*, possa levar a um dano hipocampal. [44, 50] Por outro lado, em pacientes com MDC, o dano hipocampal pode ocorrer independentemente da localização da lesão. [90] Finalmente, alguns autores sugerem que uma lesão de desenvolvimento preexistente possa predispor a crises febris ou a um SE, que por sua vez leve a um dano hipocampal com consequente ELT. [93]

Um melhor entendimento dos mecanismos associados ao dano hipocampal em pacientes com DCF poderia resultar em medidas para preveni-los, naqueles com epilepsia de início recente, assim como ajudar a identificar o melhor momento e abordagem cirúrgica naqueles com epilepsia refratária. Estudos clínico-patológicos realizados pelo grupo da UCLA expandiram o conceito de IPI introduzido por Meyer e Falconer, consolidando o conceito de que, em pacientes com ELTM-EH tratados cirurgicamente, a EH está associada a um IPI. No presente estudo, realizamos uma avaliação clínico-patológica em crianças com ELT refratária para identificar os mecanismos patogênicos do dano hipocampal em indivíduos com DCF.

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2 JUSTIFICATIVA DO TRABALHO

As displasias corticais focais são o substrato etiológico mais comum na cirurgia da epilepsia pediátrica.

A esclerose hipocampal é a alteração patológica mais encontrada em adultos jovens com epilepsia temporal refratária, compreendendo 50-70% dos casos.

Pacientes com displasia cortical focal frequentemente apresentam esclerose hipocampal, porém os mecanismos subjacentes à lesão hipocampal em tais pacientes são desconhecidos.

Um melhor entendimento dos mecanismos associados ao dano hipocampal em pacientes com displasia cortical focal poderia resultar em medidas para prevenir este dano naqueles com epilepsia de início recente, assim como ajudar a identificar o melhor momento e abordagem cirúrgica naqueles com epilepsia refratária.

No presente estudo, realizamos uma avaliação clínico-patológica em crianças com epilepsia do lobo temporal refratária para identificar os mecanismos patogênicos do dano hipocampal em pacientes com displasia cortical focal.

3 OBJETIVOS

3.1 GERAL

Investigar os mecanismos patogênicos da perda neuronal hipocampal em pacientes com displasia cortical focal.

3.2 ESPECÍFICOS

Determinar se existe relação direta entre perda neuronal hipocampal e:

- Severidade da epilepsia;
- Duração da epilepsia;
- Idade de início da epilepsia;
- Localização da epilepsia;
- Presença de injúria precipitante inicial;
- Presença de segunda patologia cerebral principal.

4 PACIENTES E MÉTODO

4.1 DESENHO DO ESTUDO

Estudo retrospectivo, tipo caso-controle, com o objetivo de investigar os mecanismos dos danos hipocampais em crianças com DCF. Os grupos de estudo (casos) incluíram pacientes com epilepsia refratária e cirurgia localizada no LT cuja análise neuropatológica revelou DCF (grupos DCF tipo I e II). Os grupos de comparação (controles) incluíram pacientes com tumores de baixo grau (grupo TBG), pacientes sem lesão neocortical com ou sem esclerose hipocampal (grupo EH/SLN) e controles de autópsia (grupo Autópsia). As variáveis clínicas foram retiradas dos prontuários e correlacionadas com a presença de danos hipocampais, avaliados por métodos qualitativos (RM e histopatologia) e quantitativos (densidades neuronais). Por fim, realizamos uma análise estatística multivariada e estratificada para controlar para possíveis variáveis de confusão.

Avaliamos um total de cento e oito crianças de zero a dezoito anos. Cinqüenta e nove crianças foram provenientes da Universidade da Califórnia, Los Angeles (UCLA), EUA, operadas entre 1996 e 2008. Trinta e nove crianças foram provenientes da Faculdade de Medicina de Ribeirão Preto (FMRP-USP), Brasil, operadas entre 2001 e 2008. Todos apresentavam epilepsia resistente aos medicamentos, definida como falha no controle completo das crises com dois FAEs apropriados usados como prescritos e aumentados para os níveis máximos tolerados. [1] Todos os controles de autópsia foram da FMRP-USP. O Consentimento Informado foi obtido para uso dos dados clínicos para estudos de pesquisa em ambas as instituições.

4.2 VERIFICAÇÃO DOS CASOS E SELEÇÃO DOS CONTROLES

Todos os pacientes incluídos neste estudo foram submetidos à cirurgia do LT, por suas avaliações pré-cirúrgicas terem sugerido o LT como local de origem das crises. O LT a ser ressecado foi definido baseado na convergência de anormalidades obtidas na monitoração por vídeo-EEG e neuroimagem (RM, FDG-PET ou SPECT). Os protocolos clínicos foram publicados previamente. [2, 3] A avaliação pré-cirúrgica incluiu história detalhada e exame neurológico, EEG de escalpo interictal e ictal e, quando necessário, injeções de amobarbital intracarotídeo (teste de Wada) ou RM funcional para a avaliação da representação da memória ou da fala, em ambas as instituições. Estudos de neuroimagem incluíram RM de 1,5T (UCLA e FMRP-USP), FDG-PET (somente UCLA), e SPECT ictal (somente FMRP-USP).

Grupo DCF: Os pacientes com ELT refratária cuja análise histopatológica do tecido ressecado revelou DCF foram incluídos neste grupo. Após revisão dos relatórios da neuropatologia, os pacientes foram qualificados de acordo com a classificação de Palmini, em DCF tipo I ou tipo II, como segue: se a análise histopatológica revelasse desorganização e deslaminação cortical ou neurônios hipertróficos sem neurônios dismórficos ou células em balão, eram classificados como DCF tipo I. Aqueles com desorganização e deslaminação cortical ou neurônios hipertróficos mais neurônios dismórficos ou células em balão, eram classificados como DCF tipo II. [4]

Grupo TBG: Os pacientes com ELT refratária cuja avaliação histopatológica revelou TBG foram incluídos neste grupo. O diagnóstico histopatológico de TBG foi definido de acordo com a classificação atual da WHO. [5]

Grupo EH/SLN: Neste grupo, incluímos todos os pacientes com ELT cuja avaliação neuropatológica não revelou nenhuma outra lesão (sem lesão neocortical) à exceção de EH. Os pacientes RM-negativos foram incluídos, se a história, o exame clínico, o monitoramento por vídeo-EEG e os estudos de neuroimagem claramente sugerissem ELT.

Grupo Autópsia: Para finalidades de comparação (controles), foi obtido tecido hipocampal de autópsia de crianças com idade similar, sem doença neurológica. O óbito, neste grupo, foi secundário a evento cardíaco agudo, sepse ou

causas traumáticas.

4.3 VARIÁVEIS

4.3.1 Métodos Qualitativos

4.3.1.1 Ressonância Magnética

As imagens de RM foram adquiridas em um *scanner* Siemens Sonata de 1,5 T (Siemens Medical Systems, South Iselin, NJ). O protocolo de RM estrutural incluiu T1 sagital (TR/TE 400/14, matriz 256x192, 5mm espessura), T1 coronal (TR/TE 25/9, TI 8, matriz 256x256, 1.8 mm espessura), T2 axial (TR/TE 3000/80, matriz 256x192, 4mm espessura), T2 coronal (TR/TE 4000/85, matriz 256 x 192, 4mm espessura),FLAIR axial (TR/TE 8000/108, TI 2000, matriz 256x192, 4mm espessura) e FLAIR coronal (TR/TE 8000/18, matriz 256x192, 4mm thickness). As imagens foram avaliadas e analisadas por um mesmo neurorradiologista (NS) para a presença ou ausência de anormalidades qualitativas hipocampais, como aumento do sinal em seqüências T2 e FLAIR e atrofia em T1.

4.3.1.2 Histopatologia Hipocampal

4.3.1.2.1 Retirada de tecido hipocampal

Depois de realizada uma ressecção temporal anterior, 1,5-2 cm de neocórtex e de substância branca adjacente foram removidos microcirurgicamente e enviados para análise imunocitoquímica. Também foram retirados 3-4 cm do hipocampo, para posterior avaliação qualitativa e quantitativa.

4.3.1.2.2 Processamento do tecido hipocampal para histopatologia

Inicialmente, alguns blocos hipocampais foram fixados com paraformaldeido a 4%, crioprotegidos em solução de sacarose a 20% e posteriormente a 30%. Os blocos foram então congelados com gelo seco e fatiados a 30µm, em criostato Mikrom (-23C) para análise histopatológica com hematoxilina-eosina (HE). As fatias foram então lavadas com água destilada e os núcleos corados com hematoxilina. Após a primeira etapa de coloração, o material foi lavado em água corrente e reidratado com solução alcoólica a 30%. Foi feita uma segunda lavagem em água corrente, para então ser corado com eosina, para análise de proteínas eosinofílicas intra e extracelulares.

4.3.1.2.3 Avaliação histopatológica do hipocampo

As fatias hipocampais foram revisadas por dois examinadores (TRV e GWM) que as classificaram como: normal (sem-EH); esclerose hipocampal clássica (EH-clássica); esclerose hipocampal severa (EH-severa); ou indeterminada. Os hipocampos sem perda celular foram classificados como sem-EH. Aqueles com perda neuronal severa no setor de Sommer (CA1 e PRO) e no endofolio (hilo e CA4), associada a alguma perda na FD e CA3, mas com preservação relativa de CA2 e SUB, foram classificados como EH-clássica. Quando a perda hipocampal neuronal apresentava-se mais severa e difusa, envolvendo subcampos geralmente preservados na EH-clássica (CA2 e SUB), eram classificados como EH-severa. Os hipocampos em que faltavam diversos subcampos e naqueles com artefatos de preparação que impediam uma classificação apropriada, foram classificados como indeterminados. Os hipocampos classificados diferentemente pelos dois examinadores foram revistos na presença de ambos para o alcance de um consenso.

4.3.2 Métodos Quantitativos

4.3.2.1 Processamento do tecido hipocampal para avaliação das densidades

Para a avaliação das densidades neuronais os hipocampos foram fatiados em seções de 10µm. As fatias foram reidratadas com solução alcoólica a 100%, 90%, 70% e após, com água destilada. A seguir, foram coradas com cresyl violeta a 0,1% e desidratadas com solução alcoólica a 70%, 90% e 100%.

4.3.2.2 Avaliação das densidades neuronais hipocampais

As contagens neuronais foram executadas por uma pessoa (MH) cega para os dados clínicos e de neuroimagem. Os procedimentos de contagem neuronal foram previamente publicados. [3] As contagens foram executadas em 400x usando uma grade ocular e os subcampos hipocampais foram contados baseados na classificação de Lorente de Nó. [6] Os subcampos avaliados foram: as células granulares da fascia dentada superior (FDS) e inferior (FDI); estrato piramidal de CA1, CA2, C3, CA4; neurônios do prosubiculo (PRO) e subiculo (SUB). Para o estrato piramidal, foram selecionados 20 quadrados de 2 x 2 (104 x 1040 µm) em sequencia e todos os núcleos dos neurônios piramidais desta região foram contados, exceto aqueles que tocavam as faces superior e direita dos quadrados. Para as células granulares menores, foi usado um quadrado de 1 x 5 (52 x 260 µm) e foram calculadas as médias das contagens sobre estas áreas (lâminas de células granulares do topo e base). As densidades neuronais foram computadas como: N (neurônios/mm^3) = A [M/(L + M)] dividido pelo volume da área da amostragem (10 µm x área da grade), onde A é o número de núcleos contados, L é o comprimento médio do núcleo e M é a espessura da seção. Os resultados foram mostrados em número de células por milímetro cúbico (céls/mm^3), refletindo estimativas do número

de neurônios por volume de unidade, e não cálculos ”absolutos” do total de neurônios por hipocampo. Pelo fato de os métodos estereológicos (para estimar o total de neurônios) requererem a presença do hipocampo inteiro, estes não foram utilizados, por não serem viáveis em espécimes cirúrgicos. Além do mais, estávamos cientes de que, devido ao encolhimento de suas somatas, induzido por lesão, os neurônios corados por Nissl poderiam ser mais difíceis de diferenciarem-se da glia circunvizinha quando comparados a métodos de coloração específicos para neurônios. Entretanto, como os tecidos de todos os grupos foram processados e contados similarmente, as diferenças estatísticas nas densidades neuronais podem ser aceitas como válidas. [3, 7, 8] Pelo fato de não termos medido a largura do estrato granuloso, baixas densidades na FD podem refletir somente a dispersão das células granulares, e não a perda neuronal verdadeira.

4.3.3 Variáveis Clínicas

Para avaliar as variáveis clínicas associadas aos danos hipocampais, os prontuários de todos os pacientes foram revisados. Os dados incluíram: idade no início das crises, idade na cirurgia, duração da epilepsia (calculada a partir do intervalo, em anos, da idade de início da epilepsia até a idade da cirurgia), gênero do paciente, freqüência mensal de crises, tipo de crises (parciais complexas ou generalizadas) e presença de um IPI. O IPI foi definido como qualquer evento médico ou incidente com provável alteração cerebral associado à perda de consciência de no mínimo 30 minutos ou alteração na cognição por mais de 4 horas. Os IPIs foram classificados como tipo crise (crise febril prolongada, *status epilepticus*) ou tipo não-crise (meningite, encefalite, ou TCE). [9] As informações foram coletadas retrospectivamente a partir das várias entrevistas pré-cirúrgicas, sem conhecimento da patologia hipocampal.

4.4 ANÁLISE ESTATÍSTICA

Para avaliar as diferenças das variáveis categóricas entre os grupos, usamos o teste do Qui-quadrado. Para obter um nível acurado de significância nas tabelas com contagens de zero célula ou nas tabelas em que mais de 20% das células apresentavam contagens menores do que cinco, usamos testes Exatos. O teste t de Student (dois grupos) e o teste de ANOVA (mais de dois grupos) foram usados para variáveis numéricas de distribuição normal, assim como seus correspondentes (testes de Mann-Whitney e de Kruskal-Walis) foram usados para variáveis de distribuição não-normal. Análises Post-hoc após testes de ANOVA foram executadas usando teste Games-Howell para variâncias desiguais. A correlação entre duas variáveis numéricas foi avaliada usando o teste de correlação de Spearman. Para controlar para viés, usamos métodos de estratificação simples ou análises multivariadas [modelo linear geral univariado (ANCOVA)]. Em alguns hipocampos, um ou mais subcampos haviam sido lesados durante o procedimento cirúrgico, resultando em dados faltantes (*missing values*). Entretanto, a análise de dados faltantes revelou que estes eventos ocorreram completamente ao acaso e não introduziram viés ao estudo (P=0.399, teste de Little's MCAR). O pacote SPSS® (versão 16.01) foi usado para a análise estatística.

4.5 ASPECTOS ÉTICOS

O protocolo de pesquisa obteve aprovação do Comitê de Ética em Pesquisa da UCLA e FMRP-USP.

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5 ARTIGO EM PORTUGUÊS

RELAÇÃO ENTRE INJÚRIA PRECIPITANTE INICIAL E DANO HIPOCAMPAL NA DISPLASIA CORTICAL FOCAL TIPO I

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RESUMO

Introdução: As displasias corticais focais (DCF) são o substrato etiológico mais comum na cirurgia da epilepsia pediátrica. Pacientes com DCF tipo I frequentemente apresentam esclerose hipocampal (EH), porém os mecanismos subjacentes à lesão hipocampal em tais pacientes são desconhecidos. Realizamos um estudo clínico-patológico para identificar os mecanismos patogênicos da lesão hipocampal em crianças com ELT refratária associada à DCF.

Métodos: Foram incluídos pacientes com epilepsia refratária operados no lobo temporal cujo exame neuropatológico revelou DCF (grupos DCF tipo I e II). Como grupos de comparação, foram incluídos pacientes com tumores de baixo grau (grupo TBG), pacientes sem lesões neocorticais com ou sem esclerose hipocampal (EH) (grupo EH/SLN) e controles de autópsia (grupo Autópsia). As variáveis clínicas foram correlacionadas com a presença de danos no hipocampo.

Resultados: Um total de 108 crianças foi incluído no estudo: 41 pacientes no grupo EH/SLN (38%), 32 no grupo FCD tipo I (29,6%), 20 no grupo TBG (18,5%), 5 no grupo FCD tipo II (4,6%) e 10 no grupo Autópsia (9,3%). A prevalência de IPI foi pequena no grupo TBG, intermediária nos grupos FCD tipos I e II e alta no grupo EH/SLN (P <0,001). A análise mostrou que, nos grupos FCD tipo I e EH/SLN, a presença de uma injúria precipitante inicial (IPI) foi associada a uma menor densidade neuronal na fascia dentada (FD) e setor de Sommer [CA1 e prosubiculo (PRO)].

Conclusão: Nossos resultados suportam a visão de que, semelhante aos pacientes com epielpsia do lobo temporal associada a esclerose hipocampal (ELTM-EH), o mecanismo de lesão hipocampal em pacientes com DCF tipo I parece estar relacionado a um IPI.

INTRODUÇÃO

As displasias corticais focais (DCF) compreendem o substrato etiológico mais comum na cirurgia da epilepsia de crianças e um dos substratos mais comuns em adultos. [1-4] De acordo com o esquema de classificação mais recente, as DCFs podem ser divididas entre: leve, tipo I e severa, tipo II. [5] O tipo I é caracterizado, exclusivamente, por desorganização e deslaminação cortical (DCF tipo IA), ou pode também incluir neurônios piramidais hipertróficos fora da camada V (DCF tipo IB). Além dos distúrbios da laminação arquitetural cortical vistos no tipo I, as DCF tipo II apresentam alterações histopatológicas importantes, incluindo neurônios dismórficos (DCF tipo IIA) ou células em balão (DCF tipo IIB). Apesar de pertencerem à mesma categoria patológica, os pacientes com DCFs tipo I e II apresentam perfis clínicos diferentes. Os pacientes com DCF tipo I apresentam, frequentemente, uma doença mais difusa, um dano cognitivo mais severo, e um pior controle das crises convulsivas no pós-operatório. [6,7] Já os pacientes com DCF tipo II, são mais jovens no início das crises, mais jovens na cirurgia, e apresentam maior frequência de crises quando comparados com aqueles com o tipo I. [8] Diferentes mecanismos patogênicos parecem estar implicados na formação dos dois tipos de DCFs. O tipo I parece ser secundário a uma organização cortical anormal adquirida em estágios avançados do desenvolvimento cortical após termino da maior parte do período de proliferação celular. Por outro lado, o tipo II, caracterizado histológicamente pela presença de células que, em estágios precoces do desenvolvimento, falharam em diferenciar-se, seria, provavelmente secundário à uma proliferação celular anormal. [2,3] Suportando esta teoria, os pacientes com DCF tipo I apresentam, mais frequentemente, epilepsia do lobo temporal (ELT), assim como história de problemas perinatais, quando comparados aos pacientes com DCF tipo II. Além do mais, o tipo I é, comumente, associado à esclerose hipocampal (EH), uma patologia, provavelmente, adquirida. [7,9] Entretanto, os mecanismos que conduzem aos danos hipocampais nas crianças com DCFs ainda não foram compreendidos completamente.

Avaliar o relacionamento entre DCF e EH é importante não somente para compreender os mecanismos dos danos hipocampais subjacentes em pacientes

com DCFs, mas também pelas consequentes implicações no manejo clínico desta patologia. Por exemplo, mostrou-se que quando ambos os substratos patológicos estão presentes, DCF mais EH (dupla patologia), a remoção cirúrgica tanto da DCF quanto da EH torna-se a melhor opção. [10,11] Sendo assim, durante a avaliação pré-cirúrgica, a identificação de características clínicas e eventos que predispõe aos pacientes com DCF a desenvolverem EH ou a identificação de características dos pacientes com EH que sugerem a presença de DCF, apontariam para a presença de uma dupla patologia, que por sua vez, levaria a uma definição mais precisa da verdadeira área epileptogênica antes do tratamento cirúrgico.

Trabalhos clínico-patológicos em crianças e adultos com ELT, realizados por nosso grupo, identificaram que os mecanismos de dano hipocampal crise-relacionados estão ligados a uma injuria precipitante inicial (IPI). Contudo, os danos hipocampais adicionais podem ocorrer devido às crises límbicas crônicas. [12-14] No presente estudo realizamos uma avaliação clínico-patológica para identificar os mecanismos patogênicos do dano hipocampal nas crianças com ELT refratária, associada à DCF.

PACIENTES E MÉTODO

Estudo caso-controle realizado para avaliar os mecanismos de dano hipocampal nas crianças com DCF. Os grupos de estudo (casos) incluíram pacientes com epilepsia refratária com cirurgia localizada no lobo temporal (LT), cuja análise neuropatológica revelou DCF (grupos DCF tipo I e II). Os grupos de comparação (controles) incluíram pacientes com tumores de baixo grau (grupo TBG), pacientes sem lesão neocortical, com ou sem esclerose hipocampal (grupo EH/SLN), e controles de autópsia (grupo Autópsia). As variáveis clínicas foram extraídas dos prontuários e correlacionadas com a presença de danos hipocampais avaliados por métodos qualitativos [ressonância magnética (RM) e histopatológica] e quantitativos (densidades neuronais).

Cinquenta e nove crianças foram provenientes da universidade da Califórnia, Los Angeles, EUA, operadas entre 1996 e 2008 (UCLA). Trinta e nove crianças foram provenientes da Faculdade de Medicina de Ribeirão Preto, Brasil, operadas entre 2001 e 2008 (FMRP-USP). Todos os pacientes apresentavam epilepsia resistente a dois fármacos anti-epilépticos apropriados (FAEs). [15] Todos os controles de autópsia foram de FMRP-USP. O consentimento Informado foi obtido para uso dos dados clínicos para estudos de pesquisa em ambas as instituições. O trabalho foi aprovado pelo Comitê de Ética em Pesquisa de ambas as instituições.

Verificação dos casos e seleção dos controles

Todos os pacientes incluídos neste estudo foram submetidos à cirurgia do LT. O LT a ser ressecado foi definido baseado na convergência de anormalidades na monitoração por vídeo-EEG e na neuroimagem. Os protocolos clínicos foram publicados previamente. [16, 17] A avaliação pré-cirúrgica incluiu história detalhada e exame neurológico, EEG de escalpo interictal e ictal, e, quando necessário, injeções de amobarbital intracarotideo (teste de Wada) ou RM funcional para a avaliação da representação da memória ou da fala, em ambas as instituições. Estudos de neuroimagem incluiram RM de 1,5T (UCLA e FMRP-USP), FDG-PET (somente UCLA) e SPECT ictal (somente FMRP-USP). Durante a cirurgia, a electrocorticografia adicional definiu a extensão das regiões cerebrais a serem

removidas (UCLA e FMRP-USP).

Grupos DCF: Os pacientes com ELT refratária cuja análise histopatológica do tecido ressecado revelou DCF foram incluídos neste grupo. Após terem sido revisados os relatórios da neuropatologia, os pacientes foram separados de acordo com o esquema da classificação de Palmini, em DCF tipo I ou tipo II, como segue: se a análise histopatológica revelasse desorganização e dislaminação cortical ou neurônios hipertróficos, sem neurônios dismórficos ou células em balão, eram classificados como DCF tipo I. Aqueles com desorganização e dislaminação cortical ou neurônios hipertróficos mais neurônios dismórficos ou células em balão, eram classificados como DCF tipo II. [5]

Grupo TBG: Os pacientes com ELT refratária cuja avaliação histopatológica revelou TBG foram incluídos neste grupo. O diagnóstico histopatológico de TBG foi definido de acordo com a classificação atual da WHO. [18]

Grupo EH/SLN: Os pacientes com ELT refratária cuja avaliação histopatológica não revelou nenhuma outra lesão à exceção de EH foram incluídos neste grupo. Os pacientes RM-negativos foram incluídos também, se a história, o exame clínico, o monitoramento por vídeo-EEG e os estudos de neuroimagem claramente sugerissem ELT.

Grupo Autópsia: Para finalidades de comparação (controles), foi obtido tecido hipocampal de autópsia de crianças com idade similar, sem doença neurológica.

Variáveis

Avaliação dos danos hipocampais

1. RM Qualitativa: As imagens de RM, executadas em um scanner de 1,5T, foram revisadas para a presença/ausência de anormalidades qualitativas hipocampais, como aumento do sinal em seqüências T2 e FLAIR e atrofia em T1.

2. Avaliação histopatológica qualitativa dos danos hipocampais: Na cirurgia, foi realizada uma ressecção temporal anterior incluindo 3-4 cm do hipocampo. As fatias hipocampais foram revisadas por dois examinadores (TRV e GWM) que as classificaram como: normal (sem-EH), esclerose hipocampal clássica (EH-clássica), esclerose hipocampal severa (EH-severa), ou indeterminada.

3. Avaliação das densidades dos neurônios hipocampais: As contagens neuronais foram executadas por uma pessoa (MH) cega para os dados clínicos e de neuroimagem. Os procedimentos de contagem neuronal foram previamente

publicados. [19] As contagens foram executadas em 400x usando uma grade. Os subcampos avaliados foram: as células granulares da fascia dentada superior (FDS) e inferior (FDI); estrato piramidal de CA1, CA2, CA3 e CA4; neurônios prosubiculares (PRO) e subiculares (SUB). Para o estrato piramidal, foram selecionados 20 quadrados de 2 x 2 (104 x 1040 µm) em sequência e todos os núcleos dos neurônios piramidais desta região foram contados; para as células granulares menores, foi usado um quadrado linear de 1 x 5 (52 x 260 µm), e foram calculadas as médias das contagens sobre estas áreas. As densidades neuronais foram computadas como: N(neurônios/mm^3) = A [M/(L + M)] dividido pelo volume da área da amostragem (10 µm x área da grade), onde A é o número de núcleos contados, L é o comprimento médio do núcleo, e M é a espessura da seção. Os resultados foram dados em número de células por milímetro cúbico (céls/mm$^{3)}$. Como os tecidos de todos os grupos foram processados e contados similarmente, as diferenças estatísticas nas densidades neuronais podem ser aceitas como válidas. [19-21]

Variáveis clínicas

Através da revisão de prontuários coletamos dados que incluíram: idade no início das crises, idade na cirurgia, duração da epilepsia, gênero do paciente, frequência mensal de crises, tipo das crises e presença e tipo de IPI conforme trabalhos prévios. [22,23]

Análise estatística

Para avaliar as diferenças entre as variáveis categóricas entre os grupos, usamos o teste do Qui-Quadrado. Para obter um nível acurado de significância usamos testes Exatos. Para variáveis numéricas, usamos o Teste t de Student (dois grupos). Os testes de ANOVA (mais de dois grupos), foram usados para variáveis numéricas de distribuição normal e os seus correspondentes (estes de Mann-Whitney e de Kruskal-Walis) para variáveis de distribuição não-normal. Análises Post-hoc após testes de ANOVA foram executadas usando teste Games-Howell para variâncias desiguais. A correlação entre duas variáveis numéricas foi avaliada usando o teste de correlação de Spearman. Para controlar para a confusão, usamos métodos de estratificação simples ou análises multivariadas [modelo linear geral univariado (ANCOVA)]. Em alguns hipocampos, um ou mais subcampos haviam sido lesados durante o procedimento cirúrgico, resultando em dados faltantes para alguns subcampos. Entretanto, a análise de dados faltantes revelou que estes eventos

ocorreram completamente ao acaso (P=0.399, teste de Little's MCAR). O pacote SPSS® (versão 16.01) foi usado para a análise estatística.

RESULTADOS

Características clínicas dos participantes do estudo

Um total de cento e oito crianças foi incluído no estudo, sendo quarenta e um no grupo EH/SLN (38%), trinta e dois no grupo DCF tipo I (29.6%), vinte no grupo TBG (18.5%), cinco no grupo DCF tipo II (4.6%) e dez no grupo Autópsia (9.3%). Os diagnósticos histopatológicos de TBG compreenderam: tumor desembrioblástico neuroepitelial (N=9), ganglioglioma/gangliocitoma (N=7) e oligodendroglioma (N=4). Cinqüenta e dois indivíduos foram do sexo feminino (48.1%). A idade média do início das crises foi de quatro anos (0,1 a 15 anos), a idade média na cirurgia foi de doze anos (1 a 18 anos), a duração média da epilepsia foi de seis anos e meio (0,5 a 16 anos), e a frequência média de crises foi de dezoito crises por mês (1 a 500). Não houve nenhuma diferença entre a idade do óbito no grupo Autópsia e a idade da cirurgia nos pacientes com ELT (diferença média = 1,8 anos, *P*=0,429, teste de Mann-Whitney). O perfil etiológico dos pacientes da UCLA foi diferente dos pacientes da FMRP-USP, com DCF tipo I sendo mais frequente nos pacientes da UCLA e EH/SLN mais frequente nos pacientes da FMRP-USP (*P*=0,008, teste Exato). Variáveis, tais como idade no início das crises, idade na cirurgia, duração da epilepsia e percentagem dos pacientes livres de crises após a cirurgia foram similares entre UCLA e FMRP-USP.

A tabela 1 mostra as características clínicas dos participantes divididos por suas categorias neuropatológicas. Os grupos foram similares em relação à idade do início das crises (*P*=0,820; ANOVA), porém a idade na cirurgia foi maior no grupo EH/SLN quando comparada aos grupos TBG e DCF tipo II (*P*=0,014; ANOVA). Isto resultou em uma duração mais baixa da epilepsia nestes grupos quando comparados ao grupo EH/SLN (*P*=0,013; ANOVA). A frequência das crises nos grupos DCF foi significativamente maior do que nos grupos EH/SLN e TBG (*P*=0,002; ANOVA). Entre todos os grupos, não houve nenhuma diferença em relação ao gênero do paciente e à proporção dos pacientes com crises parciais complexas (*P*=0,848 e *P*=0,360; respectivamente). A prevalência de IPI foi significativamente diferente entre os grupos (*P*<0,001, teste Exato), sendo baixa no grupo TBG (0%), intermediária nos grupos DCF tipo I e DCF tipo II (40% e 47%, respectivamente), e alta no grupo

EH/SLN (80%). O tipo de IPI foi similar entre os grupos. Um IPI tipo crise foi mais frequente em todos os grupos, sendo encontrado em ambos (100%) pacientes com IPI do grupo DCF tipo II, em 67% dos pacientes com IPI do grupo DCF tipo I, e em 70% dos pacientes do grupo EH/SLN (*P*=1,0, teste Exato).

Para noventa pacientes tivemos pelo menos um ano de seguimento pós-cirúrgico disponível para a análise. O tempo médio de seguimento foi de 3,6 anos (DP ± 2,7) e a percentagem total de pacientes livres de crises foi de 79%. A proporção de pacientes livres de crises foi similar entre os grupos (*P*=0,360, teste Exato), com 93% dos pacientes livres de crises no grupo TBG, 81% no grupo DCF tipo I, 80% no grupo DCF tipo II, e 72% no grupo EH/SLN.

Prevalência de dano hipocampal de acordo com a categoria neuropatológica

Avaliação qualitativa da RM

A análise das imagens de RM mostrou que a proporção de pacientes com anormalidades hipocampais no grupo EH/SLN foi elevada (93%). Dupla patologia no LT (atrofia hipocampal associada à intensidade de sinal aumentada) foi observada em uma porção razoável dos pacientes com DCF tipo I (50%) e DCF tipo II (40%), e em uma proporção pequena dos pacientes com TBG (27%, *P*<0,001, teste Exato). Para detalhes, ver tabela 1.

Avaliação histopatológica qualitativa dos danos hipocampais

Espécimes hipocampais de oitenta e cinco indivíduos estavam disponíveis para a avaliação qualitativa (79% dos casos). Similar à análise da RM, a proporção dos pacientes com EH foi significativamente diferente entre os grupos (*P*<0,001, teste Exato), com uma proporção elevada no grupo EH/SLN (80%), intermediária no grupo DCF tipo I (41%), baixa no grupo TBG (20%) e em 0% dos pacientes do grupo Autópsia. Somente três pacientes do grupo DCF tipo II tiveram os espécimes hipocampais disponíveis para a análise: dois pacientes foram classificados como sem-EH e um paciente como indeterminado. A proporção dos pacientes com EH-severa foi maior no grupo EH/SLN, quando comparada aos outros grupos (*P*<0,001, teste Exato). Para detalhes, ver tabela 1.

Tabela 1 - Caracteristicas clinicas dos pacientes divididas por suas categorias neuropatologicas

		Autopia N=10	**TBG N=20**	**DCFII N=5**	**DCFI N=32**	**EH/SLN N=41**	***P*-valor**
Idade inicio crises (media ± SD)		NA	4.8 ± 3.7	3.3 ± 3.5	4.5 ± 3.7	4.9 ± 3.4	*P*=0.820[a]
Idade cirurgia (media ± SD)		9.7 ± 6.3	9.9 ± 4.5*	8.2 ± 3.5*	11.2 ± 4.9	13.2 ± 3.5*	***P=0.014***[a]
Duração epilepsia (media ± SD)		NA	5.0 ± 3.6*	4.9 ± 2.3	6.7 ± 4.2	8.3 ± 3.9*	***P=0.013***[a]
Frequencia crises (media ± SD)		NA	51.8 ± 77	170 ± 220*	201 ± 221*	61.4 ± 132	***P=0.002***[a]
Genero(feminino) – n (%)		5 (50%)	11 (55%)	3 (60%)	13 (41%)	20 (49%)	*P*=0.848[b]
IPI (Sim) – n (%)		NA	0 (0%)	2 (40%)	15 (47%)	33 (80%)	***P<0.001***[b]
Crises parciais complexas – n (%)		NA	17 (94.4%)	5 (100%)	31 (97%)	41 (100%)	*P*=0.550[b]
Anormalidades hipocampais RM – n (%)		NA	4 (27%)	2 (40%)	16 (50%)	38 (93%)	***P<0.001***[b]
Dano hippocampal qualitativo	Sem-EH	10/10 (100%)	15/18 (80%)	2/3 (67%)	11/29 (38%)	2/36 (6%)	***P<0.001***[b]
	EH-classica	0	2/18 (13%)	0	11/29 (38%)	22/36 (61%)	
	EH-severa	0	1/18 (7%)	0	1/29 (3%)	7/36 (19%)	
	Indeterminada	0	0	1/3 (33%)	6/29 (21%)	5/36(14%)	
Livre crises apos cirurgia – n (%)		NA	14/15 (93%)	4/5 (80%)	25/31 (81%)	28/39 (72%)	*P*=0.360[b]

Avaliação quantitativa das densidades dos neurônios hipocampais.

A figura 1 mostra as densidades neuronais separadas por categorias neuropatológicas. A análise Post-hoc mostrou que as densidades neuronais foram menores no grupo EH/SLN quando comparadas com o grupo Autópsia em todos os subcampos (*P*<0,001 a *P*=0,013), exceto em SUB (*P*=0,077). Em FDS e CA1, as densidades neuronais no grupo EH/SLN foram menores do que em todos os grupos restantes. As densidades neuronais em CA4 e em CA3 foram significativamente menores no grupo DCF tipo I quando comparadas com o grupo Autópsia (*P*=0,002 e *P*<0,001, respectivamente). Em SUB, as densidades neuronais do grupo DCF tipo I foram menores do que nos outros grupos, mas não significativamente (*P*=0,077). As

densidades neuronais nos grupos TBG e DCF tipo II foram similares ao grupo Autópsia em todos os subcampos.

Assim, a avaliação dos danos hipocampais, através de estimativas qualitativas e quantitativas, revelou resultados similares. Como esperado, EH foi mais prevalente no grupo EH/SLN. Entretanto, aproximadamente 40-50% dos pacientes do grupo DCF tipo I apresentou alteração hipocampal em estudos qualitativos e diversos subcampos hipocampais deste grupo apresentaram densidades neuronais inferiores as do grupo Autópsia. A percentagem de pacientes do grupo TBG com dano hipocampal foi baixa na análise qualitativa (20-27%) e as densidades neuronais foram similares ao grupo Autópsia, na análise histopatológica quantitativa.

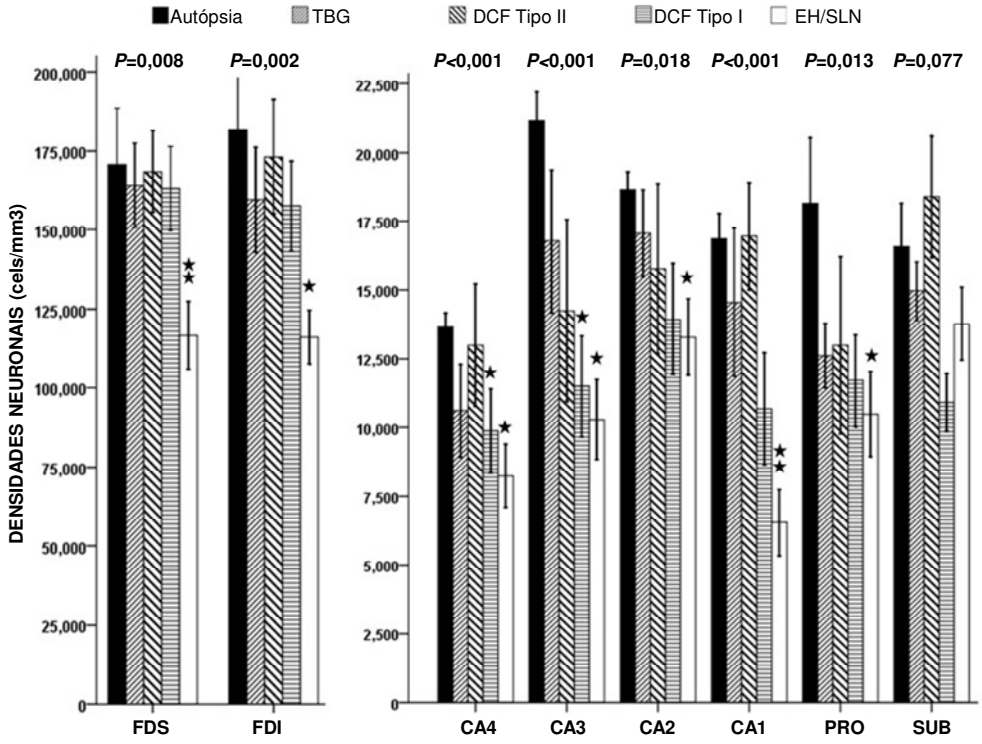

Figura 1 - O gráfico de barras mostra as densidades neuronais (média ± SEM) em subcampos específicos da formação hipocampal entre as categorias neuropatológicas. Os valores de *P* de ANOVA são mostrados acima de cada subcampo e as diferenças Post-hoc significativas são mostradas nos asteriscos (teste Games-Howell de ANOVA). As densidades neuronais foram diferentes entre os grupos em todos os subcampos ($P<0.001$ a 0.013; ANOVA), exceto SUB ($P=0.077$; ANOVA). A análise Post-hoc revelou que em FDS e em CA1, as densidades neuronais foram menores em EH/SLN do que em todas as categorias restantes ($P=0.008$ e $P<0.001$, respectivamente). Em FDI, em CA2 e em PRO, as densidades neuronais do grupo EH/SLN foram menores do que as do grupo Autópsia, mas similares às outras etiologias ($P=0.018$, $P=0.002$, e $P=0.013$, respectivamente). Em CA4 e em CA3 as densidades foram menores nos grupos EH/SLN e DCF tipo I em comparação ao grupo Autópsia ($P<0.001$). Em SUB, as densidades neuronais do grupo

DCF tipo I apresentaram uma tendência a serem menores do que nos grupos Autópsia e DCF tipo II, o que não se mostrou significante (*P*=0.077).

Correlação entre variáveis clínicas e danos hipocampais

Análise Univariada

A tabela 2 mostra a análise univariada das densidades neuronais para cada subcampo hipocampal com relação às variáveis clínicas (categoria neuropatológica, presença/ausência de IPI, duração da epilepsia, idade na cirurgia, idade do início das crises e freqüência de crises). As densidades neuronais foram associadas com a categoria neuropatológica em todos os subcampos. Correlacionaram-se também com a duração da epilepsia em FDI, CA2 e CA1; com idade na cirurgia em FDI, CA4, CA2, e CA1; e com idade do início das crises em CA4. Não houve nenhuma correlação entre a frequência das crises e densidades neuronais em nenhum subcampo hipocampal. Na maioria dos subcampos houve uma correlação entre densidades neuronais e presença de IPI (FDS, FDI, CA4, CA3, CA1 e PRO). Vale ressaltar, que todos os pacientes com EH severa pertencentes aos grupos EH/SLN e DCF tipo I apresentavam uma história positiva de IPI.

Tabela 2 - Análise Univariada da associação entre densidades neuronais hipocampais e variáveis clínicas

Subcampos	Categoria Neuropatológica[a]	IPI (sim/não)[b]	Duração Epilepsia[c]	Idade Cirurgia[c]	Idade Início Crises[c]	Freqüência Crises[c]
FDS	***P*=0.011**	***P*=0.003**	*P*=0.469	*P*=0.700	*P*=0.994	*P*=0.109
FDI	***P*=0.012**	***P*<0.001**	***P*=0.034**	***P=0.024***	*P*=0.769	*P*=0.728
CA4	***P*=0.002**	***P*=0.028**	*P*=0.066	***P*=0.004**	***P*=0.031**	*P*=0.799
CA3	***P*<0.001**	***P*=0.031**	*P*=0.295	*P*=0.078	*P*=0.062	*P*=0.800
CA2	***P*=0.018**	*P*=0.214	***P*=0.001**	***P=0.008***	*P*=0.508	*P*=0.941
CA1	***P*<0.001**	***P*<0.001**	***P*=0.007**	***P=0.018***	*P*=0.790	*P*=0.614
PRO	***P*=0.011**	***P*=0.006**	*P*=0.136	*P*=0.113	*P*=0.765	*P*=0.393
SUB	***P*=0.018**	*P*=0.448	*P*=0.544	*P*=0.074	*P*=0.435	*P*=0.745

IPI = injuria precipitante inicial, FDS = fascia dentada superior, FDI = fascia dentada inferior, CA1 a CA4 = subcampos do Corno de Ammon, PRO = prosubiculo e SUB = subiculo.
a = ANOVA de sentido único; b = teste t de Student; c = Teste de correlação de Spearmann.

Análise Multivariada

Para obter uma estimativa não enviesada dos efeitos de múltiplas variáveis independentes na variável dependente (densidade neuronal), uma análise multivariada foi realizada (Modelo linear geral-ANCOVA). As variáveis

independentes incluídas no modelo foram: categoria neuropatológica e presença/ausência de IPI como fatores; e duração da epilepsia e idade na cirurgia como cofatores (Tabela 3). Os grupos DCF tipo II e TBG foram excluídos desta análise por apresentarem um tamanho de amostra pequeno e ausência de pacientes com IPI, respectivamente. A análise mostrou que nos grupos DCF tipo I e EH/SLN a presença de um IPI esteve, independentemente, associada com baixas densidades neuronais na FDS e FDI e no setor de Sommer (CA1 e PRO), mesmo controlando para categoria neuropatológica, idade na cirurgia, e duração da epilepsia. Quando controlada para a idade na cirurgia, a duração da epilepsia não foi correlacionada com as densidades neuronais em nenhum subcampo hipocampal (ver tabela 3 para detalhes). Desta forma, a análise multivariada mostrou que a presença de um IPI foi a variável mais fortemente associada a um dano hipocampal nos pacientes com DCF tipo I e que este dano foi mais proeminente no setor de Sommer (CA1 e PRO).

Tabela 3 - Análise multivariada modelo linear geral (ANCOVA) da associação entre densidades neuronais e variáveis clínicas para os grupos DCF tipo I e EH/SLN

Subcampos	Categoria Neuropatológica	Presença IPI	Duração Epilepsia	Idade Cirurgia	Interação[a]	Modelo corrigido
FDS	***P*=0.011**	***P*=0.042**	*P*=0.401	*P*=0.173	*P*=0.099	***P*=0.004**
FDI	*P*=0.059	***P*=0.003**	*P*=0.419	*P*=0.804	*P*=0.226	***P*<0.011**
CA4	*P*=0.669	*P*=0.172	*P*=0.481	***P*=0.014**	*P*=0.669	***P*=0.019**
CA3	*P*=0.958	*P*=0.142	*P*=0.825	*P*=0.187	*P*=0.998	*P*=0.278
CA2	*P*=0.973	*P*=0.765	*P*=0.249	*P*=0.110	*P*=0.126	***P*=0.015**
CA1	***P*=0.037**	***P*=0.025**	*P*=0.413	*P*=0.461	*P*=0.899	***P*<0.001**
PRO	*P*=0.952	***P*=0.012**	*P*=0.143	*P*=0.413	*P*=0.461	***P*=0.012**
SUB	*P*=0.144	*P*=0.389	*P*=0.948	*P*=0.814	*P*=0.884	*P*=0.532

IPI = injuria precipitante inicial, FDS = fascia dentada superior, FDI = fascia dentada inferior, CA1 a CA4 = subcampos do Corno de Ammon, PRO = prosubiculo e SUB = subiculo.
a = interação entre os 2 fatores (categoria neuropatológica e presença de IPI).

Para ilustrar a associação entre IPI e densidades neuronais, separamos os pacientes com DCF tipo I e os pacientes com EH/SLN, naqueles sem ou com IPI (Figura 2). A análise estratificada mostrou que as densidades neuronais dos pacientes com DCF tipo I sem IPI foram similares à Autópsia em todos os subcampos, exceto CA3. Por outro lado, as densidades neuronais dos pacientes com DCF tipo I com IPI foram muito similares a dos pacientes com EH/SLN com IPI. De fato, a análise Post-hoc (teste Games-Howell) revelou que em FDS, FDI, CA4 e

PRO, as densidades neuronais foram menores nos pacientes com DCF tipo I com IPI quando comparadas com o grupo Autópsia. Em CA1, os pacientes do grupo EH/SLN com IPI tiveram densidades menores quando comparados com os pacientes do grupo DCF tipo I com IPI (figura 2).

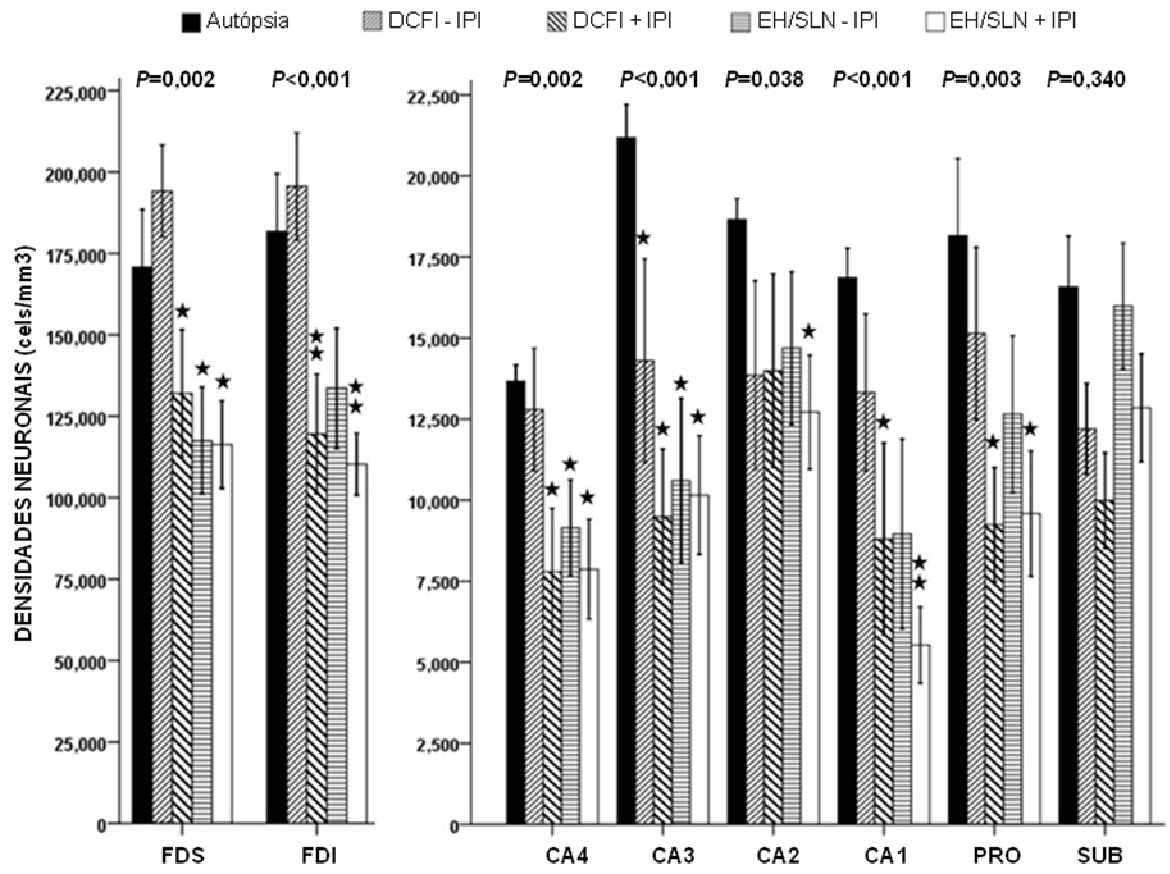

Figura 2 - O gráfico de barras compara as densidades neuronais (média ± SEM) em subcampos específicos da formação hipocampal, entre os grupos Autópsia e DCF tipo I com ou sem IPI (DCFI - IPI e DCFI + IPI) e o grupo EH/SLN com ou sem IPI (EH/SLN - IPI e EH/SLN + IPI). O padrão e a quantidade de perda neuronal hipocampal do grupo DCF tipo I com IPI foi similar ao padrão observado no grupo EH/SLN. Os valores de *P* de ANOVA são mostrados acima de cada subcampo e as diferenças Post-hoc significativas são mostradas nos asteriscos (teste Games-Howell de ANOVA). Em FDS, as densidades neuronais em ambos os grupos com IPI: EH/SLN e DCF tipo I, foram menores do que no grupo DCF tipo I sem IPI, mas similares ao grupo Autópsia. Em FDI, as densidades neuronais em ambos os grupos com IPI: EH/SLN e DCF tipo I, foram menores do que nos grupos Autópsia e DCF tipo I sem IPI, mas similar ao grupo EH/SLN sem IPI. Em CA4, as densidades neuronais no grupo DCF tipo I com IPI e em ambos os grupos EH/SLN (sem e com IPI) foram menores do que no grupo Autópsia e similares ao grupo DCF tipo I sem IPI. Em CA3, todos os grupos apresentaram densidades neuronais similares, todas menores do que o grupo Autópsia. Em CA2, as densidades neuronais do grupo EH/SLN com IPI foram menores do que o grupo Autópsia, porém similares aos grupos e DCF tipo I sem IPI, DCF tipo I com IPI e EH/SLN sem IPI. Em CA1, as densidades neuronais foram menores no grupo EH/SLN com IPI do que nos grupos Autópsia e DCF tipo I sem IPI; o grupo DCF tipo I com IPI apresentou densidades menores do que o grupo Autópsia. Em PRO, os grupos DCF tipo I com IPI e EH/SLN com IPI apresentaram densidades neuronais menores quando comparados com o grupo Autópsia.

DISCUSSÃO

Danos hipocampais são frequentemente encontrados em pacientes com DCF tipo I, e em pacientes com ELTM-EH a perda de neurônios hipocampais está provavelmente relacionada a eventos ocorridos durante a infância (IPI). [14, 24-27] Todavia, os mecanismos capazes de causarem danos hipocampais nas crianças com DCF tipo I ainda não são totalmente compreendidos. Com o intuito de esclarecer esta questão, realizamos um estudo clínico-patológico em uma série de crianças com ELT. Nossos resultados mostram que 50% das crianças com DCF tipo I apresentam danos hipocampais significativos associados à doença displásica e que 47% destas mesmas crianças apresentam uma história de IPI. Vimos que densidades neuronais hipocampais baixas estão fortemente associadas a uma história de IPI, mesmo quando controladas para outras variáveis. A perda de neurônios hipocampais não foi associada a outras variáveis clínicas, tais como frequência de crises, idade na cirurgia e duração da epilepsia.

Interpretação dos resultados do estudo

Nossos resultados estão de acordo com resultados de outros estudos, mostrando que a DCF tipo I ocorre comumente no LT em associação a EH (dupla patologia), enquanto DCF tipo II é raramente encontrada apenas no LT. [6, 7, 9, 28] A localização de lesões como DCF tipo I ou mesmo TBG no LT é uma das teorias postuladas para o desenvolvimento dos danos hipocampais em tais pacientes, pois pela sua proximidade ao hipocampo, as crises mesiais, frequentes e crônicas, poderiam resultar em perda neuronal hipocampal, enquanto crises provenientes de lesões extras temporais, não. [29] Isto explicaria porque a dupla patologia é menos encontrada nos indivíduos com DCF tipo II (raramente encontrada exclusivamente no LT). Em nossa série de pacientes, contradizendo esta teoria, porém de acordo com outros autores, os pacientes com TBG localizados no LT raramente tiveram RM ou evidência histopatológica de danos hipocampais (27%). [30]

Além disso, estudos precedentes mostraram que as MDCs estão associadas à atrofia hipocampal, independente da distância da lesão em relação à formação hipocampal. [90] Também, em nossa série de pacientes, densidades neuronais hipocampais não se correlacionaram com a frequência de crises ou com a duração

da epilepsia, sugerindo outros mecanismos para a perda neuronal que não um mecanismo exclusivamente tipo *kindling*.

O presente estudo está de acordo com outros, que mostram que é comum a ocorrência de eventos peri e pós-natais em pacientes com DCF tipo I .[6] Usando métodos quantitativos para avaliar a perda neuronal hipocampal, vimos que, em pacientes com ELT e DCF tipo I, uma história de IPI está associada a densidades neuronais hipocampais diminuídas na FD e no setor de Sommer (CA1 e PRO). Por outro lado, os pacientes do grupo TBG não tiveram nenhuma história de IPI, assim como danos hipocampais à RM e histopatologia foram incomuns (27% e 20%, respectivamente). Enquanto o grupo de pacientes com DCF tipo I sem uma história de IPI apresentou densidades neuronais hipocampais similares aos do grupo Autópsia, o grupo de pacientes com DCF tipo I com uma história de IPI apresentou um padrão da perda neuronal muito similar ao dos pacientes com EH somada a uma história de IPI (Figura 2). Sendo assim, nossos dados sugerem que o mecanismo de perda neuronal hipocampal nos pacientes com DCF tipo I esteja relacionado ao IPI, o que foi confirmado pela análise multivariada. Estes dados suportam a hipótese do segundo insulto, em que uma lesão preexistente (DCF tipo I) predispõe a posteriores eventos durante a infância (crises prolongadas ou SE), que podem resultar em dano hipocampal. [31]

Não podemos excluir que o mesmo mecanismo patogênico responsável pelo o desenvolvimento de DCF tipo I contribua para o desenvolvimento dos danos hipocampais. Acredita-se que a DCF tipo I seja secundária a eventos tardios ocorridos durante o desenvolvimento cerebral, que podem levar a uma alteração da maturação cerebral local, com consequente organização cortical anormal e células gigantes e displásicas. [4] Esta idéia é suportada por descrições prévias de desorganização citoarquitetônica, arranjo neuronal anormal e presença de neurônios hipertróficos em um córtex primeiramente não lesado de crianças com dano cerebral perinatal (displasia cortical adquirida). [32] É possível que eventos que ocorrem em períodos tardios do desenvolvimento cerebral possam resultar em ambos: DCF adquirida e dano hipocampal. Isto poderia predispor as crianças a um segundo insulto (IPI) ocorrendo mais tarde na vida, resultando em danos hipocampais adicionais. Assim, após um período latente, mudanças cerebrais envolvendo neuroplasticidade em resposta a ambos os eventos ocorreriam, tendo como resultado, excesso de excitabilidade e ELT tardia. De acordo com esta idéia existe o

fato de que, em nossa série, EH-clássica foi encontrada em pacientes sem uma história de IPI, porém todos os pacientes com EH-severa apresentaram uma história de IPI.

Em relação aos pacientes do grupo EH/SLN, este estudo mostrou que a prevalência de um IPI foi tão elevada quanto em séries de adultos. [12] Confirmou também achados anteriores, de que crianças com ELT apresentam perdas neuronais em uma quantidade e padrão similar aos adultos com ELT, com perda maior no setor de Sommer (CA1 e PRO) e CA4 poupando, relativamente, CA2. [13] Na presente série, a idade média na cirurgia dos pacientes do grupo EH/SLN foi de somente treze anos, fato que suporta a noção de que, embora alguns danos adicionais possam ser o resultado de crises límbicas crônicas, a maioria dos danos hipocampais já esta presente em estágios precoces da doença, como sugerido previamente. [11]

Limitações do estudo

As limitações do estudo são: o fato de esta ser uma série pediátrica, com um perfil clínico diferente, quando comparada a séries de adultos (idade mais baixa de início das crises e na cirurgia, frequência mais elevada de crises e períodos latentes menores). Além disso, embora tenhamos combinado a série de duas instituições para aumentar o tamanho da amostra, ainda assim, tivemos um número pequeno de pacientes para a análise de subgrupos. Pelo fato de termos realizado um estudo clínico-patológico avaliando tecido hipocampal, incluímos apenas pacientes com ELT, o que limitou nossa capacidade de fazer inferências sobre DCFs localizadas em outras regiões cerebrais, que não o LT. Estudos adicionais futuros, usando técnicas de neuroimagem volumétrica, possivelmente poderão confirmar o conceito proposto neste estudo, assim como avaliar o papel da localização das DCFs no desenvolvimento de dano hipocampal.

Devemos notar, porém, que ao incluir somente crianças com epilepsia, tivemos a oportunidade de avaliar e testar hipóteses patogênicas em estágios mais precoces da doença, o que nos permitiu confirmar conceitos gerados por estudos realizados especialmente em adultos.

Da mesma forma, como foram incluídos pacientes de dois locais diferentes, acreditamos que tenhamos aumentado a validez externa e, consequentemente, a generalização de nossos achados.

Conclusão

Nossos resultados sustentam a noção de que, similarmente aos pacientes com ELTM-EH, os danos hipocampais dos pacientes com DCF tipo I são mais provavelmente uma patologia adquirida, resultante de um IPI na infância.

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6 CONCLUSÃO

Nossos resultados suportam a idéia de que, similar aos pacientes com ELTM-EH, o mecanismo de dano hipocampal freqüentemente visto nos pacientes com DCF tipo I estaria relacionado a um IPI. Sob a perspectiva da avaliação pré-cirúrgica, nosso estudo mostrou que os pacientes com DCF tipo I associada à EH apresentam uma freqüência muito mais elevada de crises do que os pacientes com ELTM-EH isolada. Conseqüentemente, nos pacientes com atrofia hipocampal à RM, uma freqüência elevada de crises deve sugerir a presença de dupla patologia. Da mesma forma, nos pacientes com evidências de DCF à RM, a presença de EH é mais provável se uma história de IPI for identificada. Em ambas as situações, uma avaliação cuidadosa da extensão da zona epileptogênica é recomendada.

ANEXO A - ARTIGO PUBLICADO NA REVISTA EPILEPSIA

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CRITICAL REVIEW AND INVITED COMMENTARY

Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: A critical review and the UCLA experience

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Summary

Recent findings on the clinical, electroencephalography (EEG), neuroimaging, and surgical outcomes are reviewed comparing patients with Palmini type I (mild) and type II (severe) cortical dysplasia. Resources include peer-reviewed studies on surgically treated patients and a subanalysis of the 2004 International League Against Epilepsy (ILAE) Survey of Pediatric Epilepsy Surgery. These sources were supplemented with data from University of California, Los Angeles (UCLA). Cortical dysplasia is the most frequent histopathologic substrate in children, and the second most common etiology in adult epilepsy surgery patients. Cortical dysplasia patients present with seizures at an earlier age than other surgically treated etiologies, and 33–50% have nonlocalized scalp EEG and normal magnetic resonance imaging (MRI) scans. 2-(^{18}F)Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is positive in 75–90% of cases. After complete resection, 80% of patients are seizure free compared with 20% with incomplete resections. Compared with type I, patients with type II cortical dysplasia present at younger ages, have higher seizure frequencies, and are extratemporal. Type I dysplasia is found more often in adult patients in the temporal lobe and is often MRI negative. These findings identify characteristics of patients with mild and severe cortical dysplasia that define surgically treated epilepsy syndromes. The authors discuss future challenges to identifying and treating medically refractory epilepsy patients with cortical dysplasia.

KEY WORDS: Review, Malformations of cortical development, Seizure, EEG, MRI, FDG-PET, SPECT, MEG-MSI, Intracranial electrodes, Hippocampal sclerosis, Glutamate, GABA, NMDA.

In 1971, David Taylor and colleagues published a seminal paper describing a brain anomaly associated with epilepsy "distinctive enough to stand on its own" (Taylor et al., 1971). The authors described the relevant histopathology as:

> . . . localized disruption of the normal cortical lamination by an excess of large aberrant neurones scattered randomly through all but the first layer. The aberrant nerve cells stood out partly because of their numbers and their inappropriate size, and partly because of their bizarre structure. Mainly pyramidal in shape, they pointed in all

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> directions and were at times crowded together. . . . The Nissl substance, particularly that adjacent to the nucleus, tended to be unusually dense and to have a wild, tigroid appearance. . . . In seven of the 10 cases the anarchy was aggravated by the addition of malformed cells of uncertain origin with large, sometimes multiple, nuclei surrounded by an excess of opalescent, pseudopodic cytoplasm. . .. For the present, therefore, it would seem best to look on these abnormalities as a particular form of localized *cortical dysplasia* [emphasis added] in which anomalous populations of neurones, and often of glia, underlie the electrical and clinical manifestations of certain focal forms of epilepsy.

The authors acknowledged, in the Discussion, the histopathologic similarities between their lesions and cortical tubers in patients with tuberous sclerosis complex (TSC). However, they also recognized that their patients with cortical dysplasia did not show the typical radiographic, cutaneous, and somatic stigmata associated with TSC. They concluded the report by stating that the link between cortical dysplasia and TSC was "remote, if it exists at all."

Most of the cases described by Taylor and colleagues would today be classified as severe cortical dysplasia. This "new" lesion was identified in 3% of their operative epilepsy cases (Taylor et al., 1971). Cortical dysplasia, therefore, was initially considered a rare malformation of cortical development associated with epilepsy. That notion has substantially changed in the last 15 years. This is illustrated in a PubMed search of peer-reviewed publications using the terms "cortical dysplasia" and "epilepsy" (Fig. 1). From 1971, after the initial study by Taylor and colleagues, to 1990 only a few papers were published. By comparison, from 1991–2007, the number of published papers on this topic has increased dramatically. This is due in part to the increased detection of cortical dysplasia lesions with modern neuroimaging. With increased detection, it became apparent that cortical dysplasia involved a spectrum of histopathologic abnormalities ranging from mild to severe. In other words, the prevalence of cortical dysplasia in epilepsy surgery patients was higher than originally appreciated. In addition, the histopathology was frequently "open to interpretation," and only recently has cortical dysplasia been consistently graded into mild and severe types.

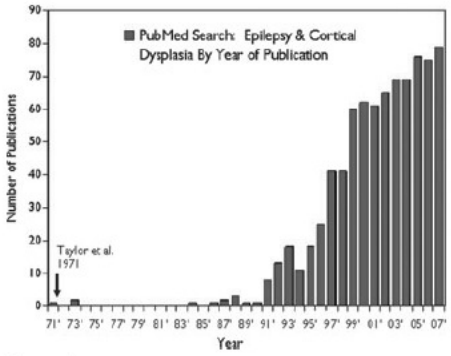

Figure 1.
Frequency histogram showing the number of articles by year of publication. PubMed was surveyed using the search terms "epilepsy" and "cortical dysplasia" and publication year, and the number of citations counted.
Epilepsia © ILAE

This review describes the clinical characteristics and outcomes for epilepsy surgery patients, with a focus on newly identified features that distinguish patients with mild Palmini type I from those with severe type II cortical dysplasia (Palmini et al., 2004). With this goal in mind, this article excludes findings on other malformations of cerebral development, such as lissencephaly, schizencephaly, TSC, hemimegalencephaly, and hypothalamic hamartoma. We emphasize findings from patients undergoing surgical resections, and do not address palliative procedures such as corpus callosotomy and neurostimulation devices. The article begins by describing the histopathologic criteria for defining mild type I and severe type II cortical dysplasia using the Palmini classification system. Next, we discuss the clinical features of patients with cortical dysplasia that distinguish them from other epilepsy surgery patients, and the different clinical characteristics of patients with mild type I and severe type II dysplasia. The next section outlines the presurgical assessment of patients with cortical dysplasia to determine the electroencephalography (EEG) and neuroimaging features and how they differ between patients with mild and severe cortical dysplasia. Mechanisms of pathogenesis and epileptogenesis obtained from studies of human cortical dysplasia tissue are briefly discussed, followed by a review of the surgical procedures and outcomes in patients with cortical dysplasia and epilepsy. Finally, we summarize the review by outlining clinical and research challenges that can guide future investigations in the diagnosis and treatment of patients with cortical dysplasia and epilepsy.

Materials and Methods

Three resources were used to accomplish the goals of this review. The first source was peer-reviewed publications obtained from a PubMed search using the terms in Fig. 1 and the added phrase "surgery." Reports of studies were included if they contained more than 20 patients, were published in English from 2002–2008 (to emphasize recent findings), contained presurgical information and

Table 1. Palmini histopathologic grading system for cortical dysplasia tissue

Grade	Severity	Histopathologic description
mMCD	Very mild vs. questionable dysplasia	Normal cortex with excess ectopic neurons in the molecular layer (layer I) or subcortical white matter
Type I	Mild	Cortical disorganization and dyslamination without abnormal dysmorphic–cytomegalic neurons or balloon cells. Type IA is cortical disorganization with no other abnormalities. Type IB is cortical disorganization with immature or hypertrophic but not dysmorphic neurons
Type II	Severe	Cortical disorganization and dyslamination with abnormal dysmorphic–cytomegalic neurons and balloon cells. Sometimes referred to as Taylor's type cortical dysplasia. Type IIA contains dysmorphic–cytomegalic neurons without balloon cells. Type IIB contains balloon cells

mMCD, mild malformation of cortical development. Sometimes termed microdysgenesis.

the number of patients seizure-free after surgery, and, if possible, separated patients into those with mild and severe cortical dysplasia (Table 1) (Palmini & Luders, 2002; Palmini et al., 2004). In addition, the studies should allow exclusion of patients with TSC, hemimegalencephaly, and coexistent tumors. They could include patients with hippocampal sclerosis and cortical dysplasia (dual pathology). If studies included patients with dual pathology we attempted to abstract data for only those patients with cortical dysplasia alone. If multiple reports from the same institution were identified, data were abstracted as if it were one cohort (Krsek et al., 2008a, 2008b). Similarly, if centers published their series over time with expanding cohorts, then the most recent studies were reviewed (Kim et al., 2000, 2008).

Twelve cohorts were identified providing data from epilepsy surgery centers in North America, Europe, Asia, and South America (Table 2; first column). Additional studies were included to supplement data for 2-(^{18}F) fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and ictal single proton emission computed tomography (SPECT) in the presurgical evaluation of patients with cortical dysplasia (Table 2), magnetic resonance imaging (MRI) features (Table 6), and predictors of surgical outcome (Table 7). Collectively these studies provide information on more than 850 epilepsy surgery patients with cortical dysplasia. By comparison, a previous review identified 64 articles published from 1971–1999 with 373 epilepsy surgery patients with cortical dysplasia and other malformations of cortical development (Sisodiya, 2000). Most of the earlier reports contained fewer than 20 patients. In the current review, the average was 72 patients per cohort with a range of 21–164 cases per center (Table 2; second column). The mean accrual per study was 9 years with a range of 3–20 years, and studies collected patients from 1986–2006 (Table 2; third column). Four studies reported mostly pediatric patients (Table 2; first four studies), two studies included a mix of pediatric and adult patients (Table 2; studies 5 and 6), and six studies were from mostly adult surgical centers (Table 2; last six studies). Two studies emphasized positive MRI scans and reported data on patients with only severe cortical dysplasia (Cohen-Gadol et al., 2004; Kral et al., 2007). Overall, for all 12 cohorts the average age at surgery was 17 years, with a range from a few months of age to 66 years (Table 2; fourth column).

The second resource was data from the University of California, Los Angeles (UCLA) Pediatric and Adult surgical programs. This cohort consisted of all patients with cortical dysplasia who had surgery from 2000–2007 (n = 97). This interval was chosen because the presurgical and neuroimaging protocols were standardized, and the histopathology was graded using the Palmini classification scheme. Excluded from the UCLA cohort were patients with cortical dysplasia operated on from 1986–1999 (n = 65) before we routinely classified patients into Palmini grades (although most were severe type II dysplasia) (Mischel et al., 1995). Also excluded were patients with mild malformations of cortical development (mMCD; Table 1), tuberous sclerosis complex (TSC), cortical dysplasia associated with tumors [e.g., dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma], hemimegalencephaly, hippocampal sclerosis, and patients who had undergone previous resective surgery. Informed consent was obtained to use data for research purposes, and the presurgical clinical protocols and operative approach have been previously published (Mathern et al., 1999; Cook et al., 2004; Cepeda et al., 2005a; Salamon et al., 2006, 2008).

The final source was a further analysis of data from 305 patients as part of the 2004 International League Against Epilepsy (ILAE) survey of 20 pediatric epilepsy surgery centers (Harvey et al., 2008). The centers were from Europe, United States, and Australia (see Appendix for investigators and locations). This analysis compared children with cortical dysplasia (n = 158) with other common etiologies in pediatric epilepsy surgery patients (n = 147; Table 3). Of note, the ILAE survey did not catalog children into those with mild and severe cortical dysplasia.

Table 2. Recent publications on surgical treatment of patients with cortical dysplasia. Cases listed by mean age of cohort (youngest to oldest)

Study/Location	N	Years	Mean age (Range)	CD % all cases	Loc interictal EEG, %	Loc Ictal EEG, %	Normal-nonspecific MRI, %	FDG-PET, %	SPECT-SISCOM, %	Intracranial electrodes, %	Comp., %	% Type I	Focal-lobar operation, %	% Sz free	% HS
Clinical studies															
Krsek et al. (2008c); Vogtareuth, Germany	40	2002–2005	7 (1–18)	N/A	32	42	10	75 (21/28)	N/A	30	N/A	60	25	42	5
Hader et al. (2004); Sick Children Toronto	39	1989–2001	10 (0.2–18)	N/A	N/A	N/A	18	92 (12/13)	N/A	38	N/A	N/A	N/A	87 (20/23)	N/A
Krsek et al. (2008a); Miami Childrens	164	1986–2006	10 (0.2–25)	29	58	77	34	N/A	N/A	48	18	57	44	55	19 (29/154)
Park et al. (2006); Seoul Nat Children's	30	1995–1999	10 (1.5–18)	58	N/A	40	26	92 (23/25)	64 (18/28)	60	26	47	80	67	N/A
Widdess-Walsh et al. (2005); Cleveland Clinic	145	1990–2002	11 (0.2–50)	N/A	N/A	63	27	N/A	N/A	40	N/A	67	80	62 (75/120)	N/A
Alexandre et al. (2006); Ribeirao Preto Brazil	41	1996–2002	19 (1–44)	8	49	71	7	N/A	48 (15/31)	34	24	39	85	63	N/A
Fauser et al. (2006, 2008); Freiburg, Germany	120	1998–2005	21 (1–66)	21	N/A	N/A	3 (2/67)	N/A	N/A	50	N/A	56	77	66 (39/59)	23
Tassi et al. (2002); Milan	52	1996–2000	24 (2–42)	23	N/A	N/A	34	N/A	N/A	67	N/A	71	81	54 (20/37)	33
Kim et al. (2008); Seoul National	145	1995–2005	25 (3–51)	15	40	76	54	69 (92/133)	57 (60/106)	86 (107/124)	9	81	80	57	19
Kral et al. (2007); Bonn, Germany	49	1989–2001	25 (5–47)	4	N/A	N/A	0	N/A	N/A	41	10	0	94	76	N/A
Cohen-Gadol et al. (2004); Yale	22	1987–2001	26 (2–58)	N/A	N/A	59	14	78 (7/9)	42 (5/12)	68	9	0	100	59	N/A
Siegel et al. (2006); Mayo Clinic	21	1993–1997	33 (18–58)	4	62	62	28	N/A	89 (8/9)	52	29	58	86	52	19
Imaging studies															
Gupta et al. (2004); Cleveland Clinic	18	1996–2000						60 (9/15)	53 (8/15)						
Kim et al. (2000); Sungkyunkwan Univ; Seoul	19	1995–1998						89 (17/19)							
Average (Totals)	72 (868)		17	14	49 (200/411)	68 (414/608)	36 (288/805)	75 (181/242)	57 (114/201)	53 (448/847)	13 (64/478)	56 (471/836)	72 (611/850)	60 (454/757)	20 (117/593)

N/A, not available. Percentage based on total N unless indicated in parentheses. Comp. complications; HS, hippocampal sclerosis; Sz, seizure.

Table 3. Comparison of pediatric epilepsy surgery patients (<18 years) with cortical dysplasia versus tumors, atrophy and hippocampal sclerosis from 2004 ILAE survey of 20 centers

Clinical variable	Cortical dysplasia (n = 158)	Tumor-atrophy-hippocampal sclerosis (n = 147)	p-Value
Age at seizure onset (years)	2.6 ± 3.4	5.1 ± 4.6	**<0.0001**
Age at surgery (years)	7.9 ± 5.3	10.7 ± 4.9	**<0.0001**
Seizure duration (years)	5.3 ± 4.5	5.5 ± 4.5	0.705
Daily seizures, %	70	48	**0.0009**
MRI positive, %	81	100	**<0.0001**
Intracranial electrodes, %	36	20	**0.0025**
Types of operations, %			
Hemispherectomy	15	17	**0.012**
Multilobar resection	23	10	
Lobar/Focal	62	73	

Data presented as mean ± SD or percentages. Modified from Harvey et al. (2008). Significant p-values ($p < 0.05$) are indicated in bold type.

Histopathology of Cortical Dysplasia: Mild Type I and Severe Type II

The key histopathologic criterion that defines cortical dysplasia is *cortical disorganization and dyslamination* (Taylor et al., 1971; Mischel et al., 1995). This consists of an irregular arrangement of cortical neurons, loss of normal cortical laminar organization, irregular clustering, and neurons showing abnormal polarity and misdirected apical dendrites (Fig. 2B, C; arrows). These histopathologic features are consistent with improper formation of the cerebral cortex and define mild cortical dysplasia. Often associated with cortical disorganization are other histopathologic findings that denote more severe abnormal cortical development. Using the UCLA cohort from 2000–2007, the other histopathologic features of cortical dysplasia, in descending order of frequency, include:

(1) Excessive *heterotopic white matter neurons*. (99% of cases) These are randomly dispersed single or groups of neurons in the subcortical white matter most often seen in regions with overlying cortical disorganization (Fig. 2B; asterisk). This finding has been attributed to abnormal neuronal migration or secondary to overproduction of cortical neurons in the periventricular proliferative zone during cerebral development (Andres et al., 2005; Mathern et al., 2007).

(2) *Dysmorphic-cytomegalic neurons*. (52% of cases) This manifests as irregularly shaped neurons that are often several times the size of normal neurons (Fig. 2D; arrow). The cytoplasm of these cells often contains neurofibrillary tangle-like cytoplasmic inclusions, irregular clumping of the Nissl substance around the nucleus, and cytoplasmic vacuolization (Vinters, 2002; Hildebrandt et al., 2005). Dysmorphic–cytomegalic neurons can be pyramidal or nonpyramidal, and a proportion of cytomegalic neurons are γ-aminobutyric acid (GABA)ergic (Andre et al., 2007). These neurons are thought to have been improperly formed in the periventricular proliferative zone during initial neurogenesis or are remnants of cells that reside in the normal human subplate that failed to undergo cell death during later phases of cortical development (Barkovich et al., 2005; Cepeda et al., 2005b).

(3) *Balloon cells*. (40% of cases) These consist of large abnormal cells with abundant opalescent eosinophilic cytoplasm and eccentric nuclei (Fig. 2E; arrow). Balloon cells may be immunoreactive for proteins associated with glia and neurons, but they have more morphologic characteristics of glial cells (Kerfoot et al., 1999; Cepeda et al., 2003). Like dysplastic neurons, these cells are thought to be abnormally formed, early generated cells or residual radial glial typically found during normal cortical development (Ying et al., 2005; Cepeda et al., 2006; Lamparello et al., 2007).

(4) Excessive *heterotopic neurons in the cortical molecular layer*. (40% of cases) This histologic feature of the normal developing cerebral cortex is considered a sign of abnormal cortical development if identified in the postnatal brain (Dehay & Kennedy, 2007). This feature consists of excessive numbers of neurons in layer I of the cerebral cortex, some of which are probably Cajal-Retzius cells (Thom et al., 2003).

(5) *Marginal and nodular glioneuronal heterotopia*. (30% of cases) Marginal heterotopia consists of (usually disorganized) neuroglial tissue extruding through the pial surface into the subarachnoid space. Nodular heterotopia can be large collections of neuroglial tissue dispersed in the cortex and white matter. Both are signs of severe cortical dysplasia and probably represent abnormal migrations of neurons and glia during cerebral development.

(6) *Polymicrogyria*. (27% of cases) This consists of multiple folds of cortical neurons, often with a fused unlayered pial surface. It is usually associated with severe cortical dysplasia, probably from overproduction of late generated neurons residing in upper cortical layers (Andres et al., 2005). Polymicrogyria generally appears as thickened cortex on MRI (Salamon et al., 2006).

(7) *Immature neurons*. (15% of cases) These are round or oval cells with a large immature nucleus and thin rim of cytoplasm. These cells are often found in clusters, and mostly in younger patients with cortical dysplasia (Cepeda et al., 2007). The presence of immature neurons is considered a sign of incomplete cortical development in the postnatal human cortex.

(8) Persistence of the *subpial or superficial granular cell layer (SGL)*. (8% of cases) The SGL is normal during

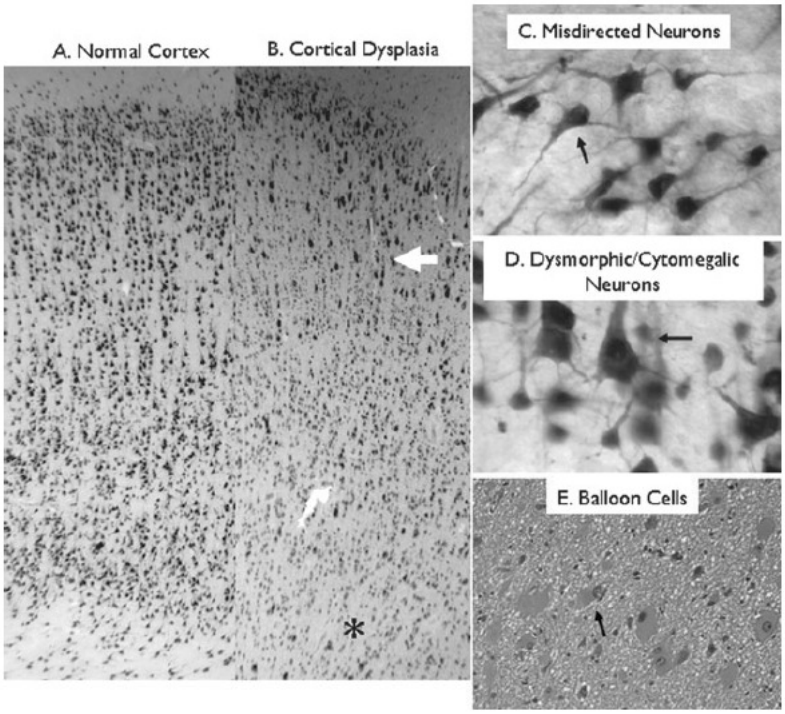

Figure 2.
Histopathology of cortical dysplasia. In all panels the pial surface is toward the top of the micrographs. Mild Palmini type I cortical dysplasia consists of cortical dyslamination and columnar disorganization (Panel B; white arrow) almost always associated with increased density of subcortical white matter neurons (Panel B; asterisk) compared with normal cortex (Panel A). Mild cortical dysplasia often contains misdirected neurons in which the cell body and primary dendrite point in a direction away from the pial surface (Panel C; arrow). Severe Palmini type II cortical dysplasia consists of cortical disorganization plus the presence of abnormal dysmorphic cytomegalic neurons (Panel D), or balloon cells (Panel E). Cytomegalic neurons are large cells in which the soma is two to three times the size of adjoining normal pyramidal neurons, with increased neurofilaments within the cell body (Panel D; arrow). Balloon cells are large cells with an eccentrically placed nucleus and astrocyte-like features including "gemistocytic cytoplasm" (Panel E; arrow). Panels A–D are stained with NeuN and Panel E with Hematoxin and Eosin (H&E).

cortical development, found in midgestation, and disappears before birth. In the postnatal brain, this is a sign of abnormal cortical development. The SGL is thought to produce GABAergic neurons during human cortical development (Bystron et al., 2008). In patients with cortical dysplasia, the SGL is often seen in a patchy distribution.

(9) Other histopathologic features that are not specific for abnormal cortical development but are often identified in association with cortical dysplasia include: Chaslin's gliosis (92%), cortical and white matter calcifications (37%), encephalomalacia, and white matter gliosis (27%).

Classification schemes have been proposed to catalog patients with cortical dysplasia into subgroups based on histopathologic and neuroradiologic criteria (Mischel et al., 1995; Raymond et al., 1995; Tassi et al., 2002; Palmini et al., 2004; Barkovich et al., 2005). The classification proposed by Palmini and Luders is the one currently used by many surgical centers and the one under evaluation in this review (Table 1). It divides patients into those

with mild type I and severe type II cortical dysplasia, with two subgroups within each major class (Palmini & Luders, 2002; Palmini et al., 2004). The main distinction between mild type I and severe type II cortical dysplasia is the presence of dysmorphic–cytomegalic neurons and balloon cells. Other characteristics of the malformed cerebral cortex are not components of the Palmini classification system (see Critical Review). Another category, termed mMCD or microdysgenesis, consists of normal cortical organization with an excess of neurons in the subcortical white matter or molecular layer. Without cortical disorganization and dyslamination, it is controversial whether mMCD represents a ''true'' form of cortical dysplasia (Kasper, 2005). With the exception of our discussion on dual pathology and hippocampal sclerosis, for the most part we exclude discussions of mMCD in this review.

Clinical Characteristics of Epilepsy Surgery Patients with Cortical Dysplasia

As a group, patients with cortical dysplasia are younger at seizure onset and surgery and have greater seizure frequency compared with most other etiologies in epilepsy surgery patients. In the 2004 ILAE survey of 20 pediatric epilepsy surgery centers, cortical dysplasia was the most frequent etiology in patients younger than age 18 years (Fig. 3A; blue bar). In pediatric epilepsy surgery patients, the next most common substrates were tumors, infections and ischemic stroke (atrophy/stroke), and hippocampal sclerosis (Fig. 3A; green, orange, and red bars). By comparison, cortical dysplasia was the third most common etiology behind hippocampal sclerosis and tumors in a report of mostly adult epilepsy surgery patients (Fig. 3B) (Becker et al., 2006). In other reports, cortical dysplasia was the second most common etiology in mostly adult epilepsy surgery patients (Raymond et al., 1995; Semah et al., 1998). In the 2004 ILAE survey of pediatric centers, children with cortical dysplasia were younger at seizure onset and surgery compared with those with tumors, atrophy/stroke, and hippocampal sclerosis (Table 3). In addition, 70% of pediatric patients with cortical dysplasia had daily seizures compared with 48% of children with other substrates (Table 3).

In published studies, patients with cortical dysplasia made up 14% of all patients undergoing epilepsy neurosurgery (Table 2; fifth column). Cortical dysplasia was a more common etiology in studies with younger cohorts (Table 2; 32–58%) compared with older cohorts (4–23%). In the UCLA cohort from 2000–2007, cortical dysplasia was found in 21% of combined adult and pediatric epilepsy surgery patients, and was the second most common etiology behind hippocampal sclerosis. In the UCLA cohort, those with cortical dysplasia had a younger age at seizure onset and surgery compared with patients with hippocampal sclerosis and mesial temporal lobe epilepsy (Fig. 4A–D). In fact, in the UCLA series, the age at seizure onset was 1 year or less in 48% of patients with cortical dysplasia (median 1.3 years). This compares with a median age of seizure onset of 11 years for patients with hippocampal sclerosis (Fig. 4C). Furthermore, in the UCLA cohort, the incidence of cortical dysplasia by age at surgery was highest in younger patients (Fig. 4E). Cortical dysplasia was the histopathologic substrate in 75% of infants and children operated upon in the first 2 years of life, compared with less than 10% in those having surgery at an age older than 21 years (Siegel et al., 2005). Similar findings were reported in the 2004 ILAE of pediatric epilepsy surgery centers, where cortical dysplasia was found in 67% of children operated on in the first year of life compared with 25% in those aged 15–18 years (Harvey et al., 2008).

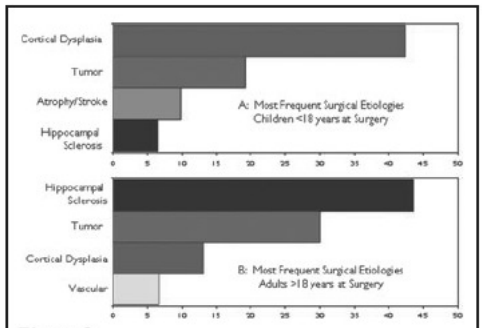

Figure 3.
Most frequent etiologies in pediatric (<18 years at surgery; top graph) and adult (>18 years; bottom graph) cohorts of patients undergoing epilepsy surgery. (**A**) In children and adolescents, cortical dysplasia is the most frequent etiology (42%) followed by tumor (19%), atrophy/stroke (infections and other forms of brain damage; 10%), and hippocampal sclerosis (6%). (**B**) In adults, hippocampal sclerosis is the most common etiology (43%), followed by tumor (30%), cortical dysplasia (13%), and vascular [cavernous malformations, arteriovenous malformation (AVM), etc.; 7%].
Epilepsia © ILAE

Characteristics of Patients with Mild Type I and Severe Type II Cortical Dysplasia

Most studies report that patients with severe type II cortical dysplasia are younger at presentation compared with those with mild type I cortical dysplasia (Palmini et al.,

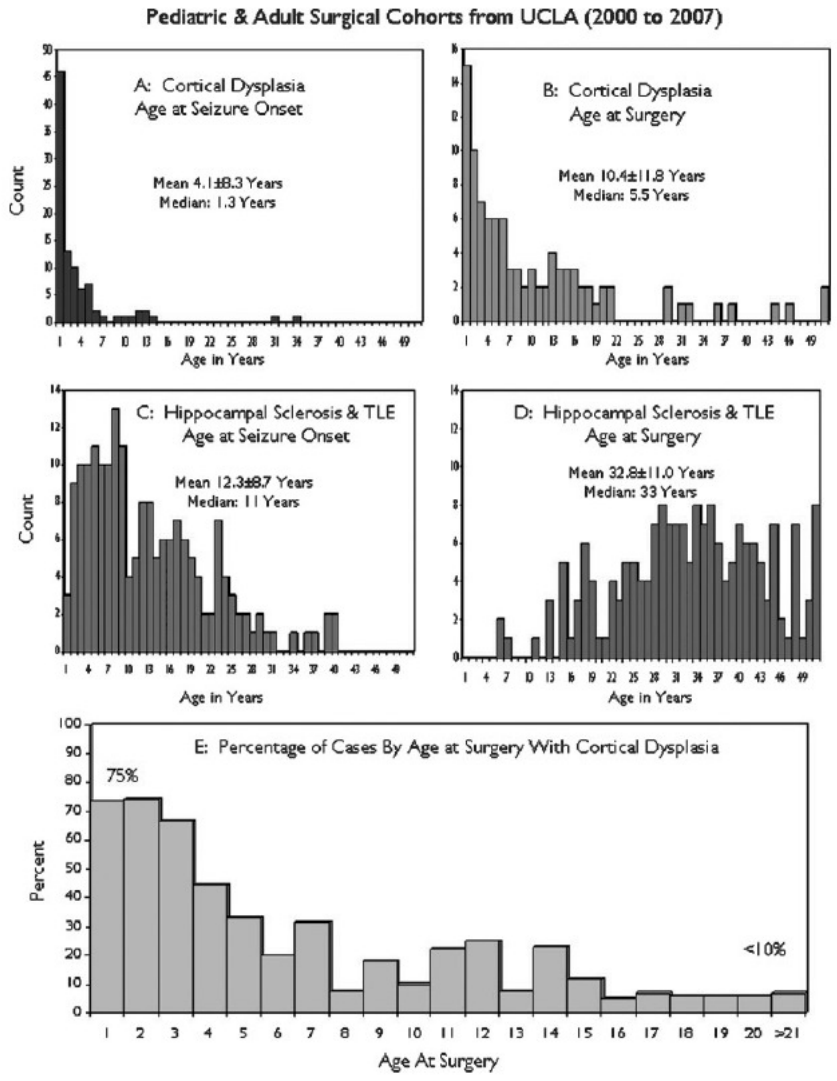

Figure 4.
From the UCLA pediatric and adult surgical cohorts, frequency histograms showing (**A**) age at seizure onset and (**B**) age at surgery for patients with cortical dysplasia compared with those with (**C**) hippocampal sclerosis and (**D**) temporal lobe epilepsy (TLE). Mean [years ± standard deviation (SD)] and median data are also shown. The age at seizure onset and surgery is younger for patients with cortical dysplasia compared with those with hippocampal sclerosis (*t*-tests; $p < 0.0001$). (**E**) Histogram indicating the percentage of patients with cortical dysplasia by age at surgery. At younger than age 3 years, more that 66% of cases had cortical dysplasia compared with less than 10% for patients older than age 21 years.
Epilepsia © ILAE

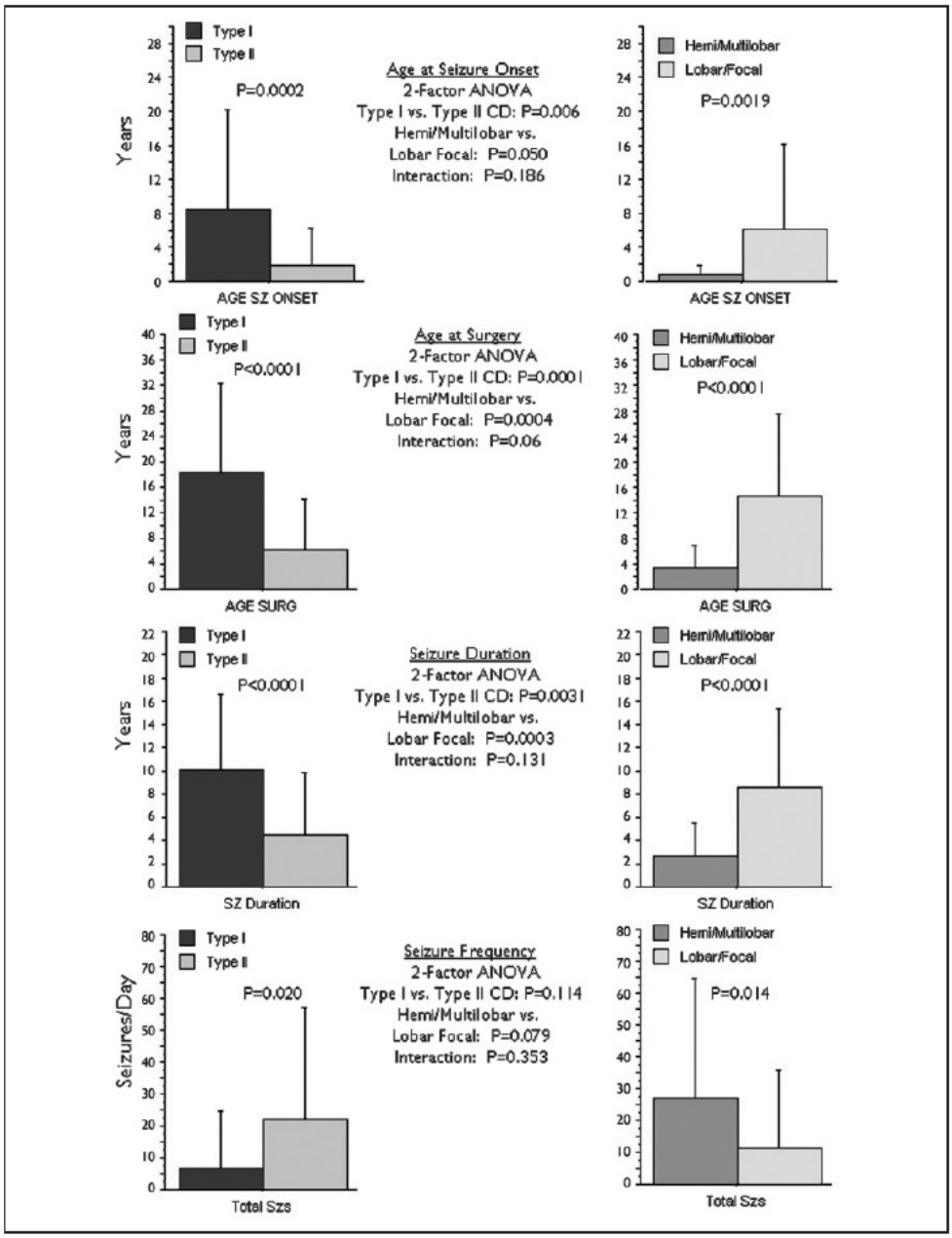
Type I
Type II
Age at Seizure Onset
2-Factor ANOVA
Type I vs. Type II CD: P=0.006
Hemi/Multilobar vs.
Lobar Focal: P=0.050
Interaction: P=0.186
P=0.0002
Years
AGE SZ ONSET
Hemi/Multilobar
Lobar/Focal
P=0.0019
AGE SZ ONSET
Age at Surgery
2-Factor ANOVA
Type I vs. Type II CD: P=0.0001
Hemi/Multilobar vs.
Lobar Focal: P=0.0004
Interaction: P=0.06
P<0.0001
AGE SURG
P<0.0001
AGE SURG
Seizure Duration
2-Factor ANOVA
Type I vs. Type II CD: P=0.0031
Hemi/Multilobar vs.
Lobar Focal: P=0.0003
Interaction: P=0.131
P<0.0001
SZ Duration
P<0.0001
SZ Duration
Seizure Frequency
2-Factor ANOVA
Type I vs. Type II CD: P=0.114
Hemi/Multilobar vs.
Lobar Focal: P=0.079
Interaction: P=0.353
P=0.020
Seizures/Day
Total Szs
P=0.014
Total Szs

Figure 5.
From the pediatric and adult UCLA surgical cohorts with cortical dysplasia, bar graphs showing mean [years ± standard deviation (SD)] age at seizure onset (top row; Age Sz Onset), age at surgery (2nd row: Age Surg), seizure duration (3rd row; Sz Duration), and seizure frequency (bottom row; Total Szs). The left column compares patients with mild Palmini type I (red bars) and severe Palmini type II (blue bars) cortical dysplasia, and the right column patients with hemispheric and multilobar operations (orange bars) and those with lobar and focal resections (yellow bars). T-test results are indicated above each bar graph. The results of the two-factor analysis of variance (ANOVA) are shown between the graphs. Patients with hemispheric/multilobar and type II cortical dysplasia were younger at age at seizure onset and surgery (top two rows; $p < 0.002$), had shorter seizure duration (third row; $p < 0.0001$), and higher frequency of seizures per day (bottom row; $p < 0.02$) compared with lobar/focal cases with type I cortical dysplasia.

2004; Fauser et al., 2006). Similarly, patients with larger areas of brain involvement by MRI are reported to have a younger age at presentation compared with those with smaller lesions in patients with mild and severe cortical dysplasia (Cepeda et al., 2006). These two findings are illustrated using the UCLA cohort (Fig. 5). Patients with severe Palmini type II cortical dysplasia had a younger age at seizure onset, younger age at surgery, shorter epilepsy duration, and increased seizure frequency compared with those with mild Palmini type I dysplasia (Fig. 5; left column; $p < 0.02$). Likewise, for both type I and type II cortical dysplasia, patients with multilobar and hemispheric areas of cortical dysplasia by neuroimaging had a younger age at seizure onset, younger age at surgery, shorter epilepsy duration, and increased seizure frequency compared with those with focal and lobar cortical dysplasia (Fig. 5; right column; $p < 0.014$). Results of a two-factor analysis of variance (ANOVA) found that higher Palmini grade and larger MRI size were both associated with a younger age at seizure onset, younger age at surgery, and shorter epilepsy duration without significant interactions (Fig. 5; middle boxes). In other words, increased severity of cortical dysplasia by histopathologic grade and larger size by neuroimaging were independent factors associated with a younger age at presentation in patients with cortical dysplasia.

The Palmini histopathologic grade is associated with other clinical factors in patients with cortical dysplasia. The literature and the UCLA series show that patients with mild Palmini type I cortical dysplasia are associated with seizures arising more frequently from the temporal lobe (Table 4) (Tassi et al., 2002; Bautista et al., 2003; Fauser et al., 2004; Widdess-Walsh et al., 2005). By comparison, patients with severe Palmini type II cortical dysplasia are more likely to have multilobar and hemispheric cortical dysplasia that involves extratemporal cortical regions, especially the frontal lobe (Table 4). Likewise, a history of infantile spasms is more common in patients with severe type II compared with mild type I cortical dysplasia (Table 4) (Lortie et al., 2002; Koh et al., 2005; Fauser et al., 2006; Krsek et al., 2008a, 2008c). Hence, infants and children are more likely to have multilobar or hemispheric lesions that on histopathology will show severe Palmini type II cortical dysplasia. Older patients can present with type II cortical dysplasia, but the lesions are likely to be small on MRI. However, for older patients, the more typical presentation is that of someone with temporal lobe epilepsy from focal or lobar disease by MRI and mild type I dysplasia on histopathology.

Presurgical Evaluation

The presurgical evaluation for patients with cortical dysplasia is often challenging. Cortical dysplasia patients often present with variable epilepsy-related symptoms depending on the age at presentation, and the location and size of the lesion. In addition, EEG and MRI may not localize to the lesion. Therefore, multiple diagnostic modalities are usually necessary to detect areas of cortical dysplasia in the presurgical evaluation of patients with intractable epilepsy.

Semiology

There is no particular seizure semiology that characterizes patients with mild and severe cortical dysplasia compared with other epilepsy surgery patients. Patients with cortical dysplasia can present with focal ictal behavioral signs and symptoms referable to any lobe of the brain. The seizures may suggest involvement of multiple lobes or a cerebral hemisphere, or present with bihemispheric features. Generalized clinical and EEG features are often characteristic of younger patients with cortical dysplasia and other etiologies (Chugani et al., 1990; Cross et al., 2006; Wyllie et al., 2007). Hence, clinicians cannot diagnose that a patient has cortical dysplasia or whether they have mild or severe dysplasia based exclusively on ictal semiology.

Scalp EEG

There are no distinctive interictal or ictal scalp EEG "signatures" that are exclusively associated with cortical

Table 4. From pediatric and adult patients at UCLA, clinical, EEG, neuroimaging, and outcome characteristics in patients with type I and type II cortical dysplasia (2000–2007)

Clinical variable	All CD cases (n = 97), %	Type I (n = 33), %	Type II (n = 64), %	p-Value (Type I vs. II)
Side-right	48	61	42	0.08
Gender—Female	49	67	41	0.05
Type of epilepsy				
Temporal lobe epilepsy	22	58	5	**<0.0001**
Extratemporal/nonhemi	45	32	51	
Hemispheric epilepsy	33	10	44	
Type of surgery				
Hemispherectomy	14	6	19	**0.0024**
Multilobar resection	23	6	31	
Lobar resection	31	48	22	
Focal resection	32	39	28	
Lobe involved				
Frontal	50	31	58	**0.0195**
Temporal	54	65	50	0.19
Parietal	46	31	53	0.05
Occipital	24	11	29	0.08
History of infantile spasms	27	15	41	**0.0191**
Status epilepticus @ surgery	16	9	20	0.16
Interictal scalp EEG				
Focal/regional discharges	47	42	50	0.61
Focal background slowing	81	62	93	**0.011**
Spike trains/CEDs	64	37	78	**0.007**
Ictal scalp EEG				
Focal/regional onsets	44	46	44	0.89
MRI-positive	78	63	98	**0.0041**
MRI feature (see Fig. 5)				
Thick gray matter	24	7	67	**<0.0001**
Blurred gray–white junction	59	14	73	**<0.0001**
Decreased T2 white matter	27	11	41	**0.0003**
Increased T2 gray matter	58	7	35	0.44
Increased T2 white matter	36	56	59	0.89
Cortical atrophy	19	21	18	0.79
FDG-PET positive	98	97	98	0.14
Intracranial electrodes	6	10	1	**0.0085**
Postsurgery seizure free	80	74	82	0.36

CEDs, continuous epileptiform discharges. Significant p-values ($p < 0.05$) are indicated in bold type.

dysplasia in patients with refractory epilepsy. The EEG can show interictal background slowing, interictal spikes and polyspikes, and ictal events with electrographic characteristics similar to other patients with intractable epilepsy who are undergoing presurgical evaluation (Noachtar et al., 2008). In fact, if there is a characteristic it is that interictal and ictal EEG findings often do not localize to the MRI-identified lesion in patients with cortical dysplasia. In the published literature, interictal findings were reported to localize to one region on scalp EEG in 49% of patients with cortical dysplasia (Table 2; sixth column; 32–62%). Likewise, ictal findings localized to one region on scalp EEG in 68% of epilepsy surgery patients with cortical dysplasia (Table 2; seventh column; 42–77%). Similar findings were found in the UCLA cohort (Table 4). Focal or regional interictal scalp EEG findings were noted in 47%, focal background slowing in 81%, interictal spike trains or continuous epileptiform discharges (CEDs) in 64%, and focal ictal onsets in 44% of epilepsy surgery patients with cortical dysplasia.

The published literature and data from the UCLA series also indicate that there are no consistent EEG findings that differentiate patients with mild type I from severe type II cortical dysplasia (Krsek et al., 2008a, 2008c). For example, in the UCLA cohort, patients with severe type II cortical dysplasia compared to those with mild type I dysplasia were more likely to have interictal EEG focal background slowing and spike trains, but there were no differences in the incidence of localized interictal epileptiform discharges and ictal onsets (Table 4). Of note, another study recently reported that EEG slowing was more common in patients with mild type I compared with severe type II cortical dysplasia (Krsek et al., 2008c). In addition, UCLA patients with focal and lobar areas of cortical dysplasia by MRI were just as likely to present with localized interictal and ictal EEG findings as patients with more

Table 5. Localized interictal and ictal scalp EEG findings based on MRI size of cortical dysplasia from pediatric and adult UCLA surgical cohort

EEG feature	Multilobar/ Hemispherectomy, %	Lobar/ Focal, %	p-Value
Interictal EEG localizing	50	50	0.99
Ictal EEG localizing	75	50	0.14

diffuse multilobar and hemispheric cortical dysplasia (Table 5). Hence, scalp EEG studies may localize interictal and ictal abnormalities to the eventual area of resection in only 50–68% of patients with cortical dysplasia undergoing presurgical evaluation, and do not distinguish patients with mild and severe cortical dysplasia (Raymond et al., 1995).

Structural MRI

There are several features on structural MRI that identify areas of cortical dysplasia in intractable epilepsy patients (Sankar et al., 1995; Yagishita et al., 1997; Lee et al., 1998; Tassi et al., 2002; Colombo et al., 2003; Raybaud et al., 2006; Widdess-Walsh et al., 2006). The MRI findings include: (1) Increased thickness of the cortical gray matter, often with abnormal gyral patterns (Fig. 6A; arrow); (2) blurring of the gray–white matter junction (Fig. 6D; arrow); and (3) increased T2 and fluid attenuated inversion recovery (FLAIR) signal intensity in the subcortical white (Fig. 6B, 6E and 6F; arrows) and gray matter (Fig. 6C; arrow). MRI white matter abnormalities can extend to the ventricle, termed "transmantle dysplasia" (Barkovich et al., 1997) (Fig. 6E; arrow). Cortical and white matter atrophy, calcifications, and contrast enhancement within the lesion have been reported but are not specific MRI features for cortical dysplasia (Bronen et al., 1997; Urbach et al., 2002).

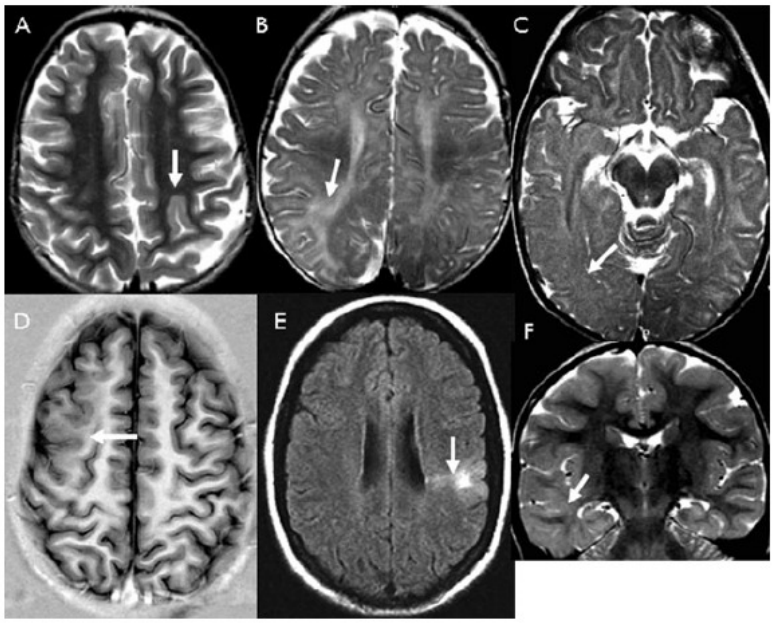

Figure 6.
Magnetic resonance imaging (MRI) features of cortical dysplasia. Qualitative MRI findings can include (**A**) thickened gray matter (arrow), (**B**) T2 hyperintensity in the subcortical white matter (arrow), (**C, F**) T2 hyperintensity of the gray matter (arrow), (**D**) blurring of the gray–white matter junction (arrow), and (**E**) transmantle sign (arrow).
Epilepsia © ILAE

When present, the constellation of MRI findings is diagnostic for cortical dysplasia in patients with intractable epilepsy. However, MRI findings can often be subtle and difficult to detect, especially for patients with mild type I and those with very small foci of severe type II cortical dysplasia (Figs. 7 and 8). In published studies, structural MRI was reported as normal or not specific for the diagnosis of cortical dysplasia in a substantial proportion of patients (Table 2; eighth column). This ranged from 100% abnormal MRI scans from Bonn, Germany, where all cases had type II cortical dysplasia (Kral et al., 2007) to 54% normal MRI scans in the adult series from Seoul, Korea, where many patients had type I cortical dysplasia (Kim et al., 2008). In the 2004 ILAE survey, 19% of children with cortical dysplasia had normal or subtle MRI scans compared with 0% for those with tumors, stroke, and hippocampal sclerosis (Table 3). In the UCLA series, 22% of patients with cortical dysplasia had normal MRI scans (Table 4). Of note, the original report by Taylor and colleagues described lesions that were not visible on gross macroscopic evaluation of the cortical specimen in six (60%) of their surgical specimens (Taylor et al., 1971).

Normal MRI scans are reported more frequently in patients with mild type I (36% and 37%) compared with severe type II cortical dysplasia (2% and 15%; Tables 4 and 6). Put another way, in recent studies 51% (85 of 166; range 7–94%) of patients with normal MRI scans at the time of surgery were found to have cortical dysplasia on histopathology (Chapman et al., 2005; Lee et al., 2005; McGonigal et al., 2007). In published studies and the UCLA series, MRI features of cortical dysplasia such as increased gray matter thickness, blurring of the gray–white junction, and increased T2 signal in the white matter were more often associated with severe type II compared with mild type I cortical dysplasia (Tables 4 and 6). By comparison, encephalomalacia and periventricular leukomalacia were more frequently reported in patients with mild type I cortical dysplasia (Tables 4 and 6) (Krsek et al., 2008c). However, no MRI features, except transmantle sign, were specific for severe cortical dysplasia. The transmantle sign has been reported in only 34% of patients with type II cortical dysplasia (Table 6). Hence, although MRI can identify cortical dysplasia in patients with refractory epilepsy with high specificity, this imaging modality does not detect a substantial proportion of individuals with mild type I and a few with severe type II cortical dysplasia in small foci.

FDG-PET, ictal SPECT, and MEG-MSI

With patients presenting with nonlocalized scalp EEG and normal MRI, many centers incorporate additional functional and neuroimaging studies into the multimodality presurgical evaluation to increase the detection of patients with cortical dysplasia. Of these tools, FDG-PET has been shown to be one of the more sensitive techniques

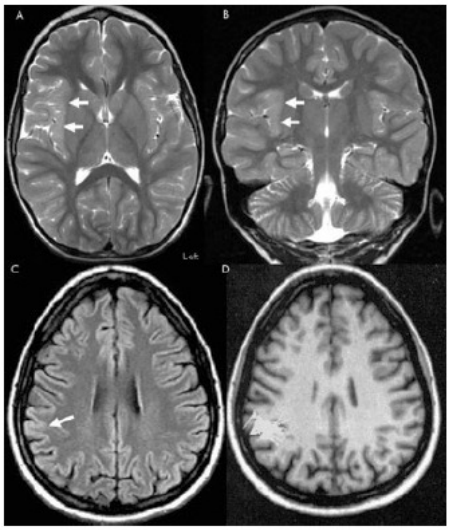

Figure 7.
Difficult to identify extratemporal severe type II cortical dysplasia by magnetic resonance imaging (MRI) in two patients. (**A, B**) This 4-year-old presented with seizures beginning at age 17 months. The seizures were characterized by tonic events involving the left body lasting usually less than a minute. The seizures could cluster resulting in status epilepticus. With the severe cluster of seizures there would be a left-sided Todd's paralysis that could last for weeks. Interictal and ictal electroencephalography (EEG) showed abnormalities over the right hemisphere that were nonlocalizing. The MRI shows an area of thickened cortex involving most of the right insula (arrows). Histopathology showed a type II dysplasia without balloon cells. This child has been seizure free after a right cerebral hemispherectomy. (**C, D**) This 19-year-old presented with seizures at age 9 years that involved left upper extremity tonic events. Interictal and ictal EEG findings localized to the Cz and C4 electrodes. Numerous MRI scans had been interpreted as normal, although a subtle change was noted over one gyrus (**C**; arrow). Magnetoencephalography (MEG)–magnetic source imaging (MEG-MSI) localized a cluster of interictal spikes over the right frontal parietal region (**D**; cluster of yellow marks). Histopathology disclosed type II cortical dysplasia with balloon cells. This person has been seizure free postsurgery after a focal cortical resection.
Epilepsia © ILAE

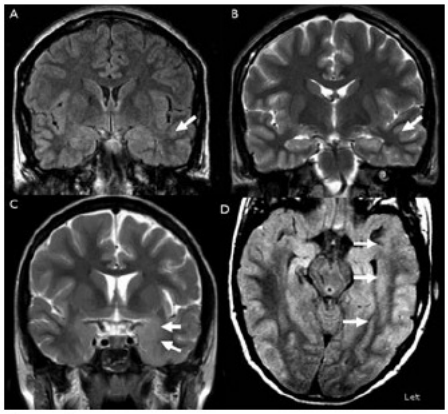

Figure 8.
Difficult to identify type I cortical dysplasia. All patients had temporal lobe epilepsy, and have been seizure free after temporal lobe resection. (**A, B**) This 15-year-old began with seizures at age 2 years, had failed 12 antiepilepsy drugs (AEDs), and averaged two to three seizures per week. Numerous previous magnetic resonance imaging (MRI) scans had been reported as normal. UCLA MRI showed subtle loss of signal (white arrows) in the left temporal white matter more easily visible on the fluid attenuated inversion recovery (FLAIR) (Panel A) than T2 (Panel B images; compare right and left sides). Histopathology showed Palmini type IA cortical dysplasia and excessive white matter neurons without hippocampal sclerosis. (**C**) This 12-year-old began with seizures at age 9 years and had many events per day. The left mesial temporal region showed an ill-defined fullness without contrast enhancement (arrows). Histopathology showed Palmini type IIA (without balloon cells). (**D**) This 10-year-old began with seizures at age 1.5 years. Scalp electroencephalography (EEG) showed bi-temporal interictal abnormalities and ictal onsets. MRI showed loss of white matter signal on FLAIR imaging involving the left temporal and posterior temporal regions extending into the occipital lobe (arrows). Surgery involved an extended left temporal resection avoiding the speech areas. Histopathology showed Palmini type IA cortical dysplasia.

in identifying areas of cortical dysplasia (Chugani et al., 1990; Cohen-Gadol et al., 2004). Contemporary studies indicate that FDG-PET detects interictal hypometabolism localized to areas of cortical dysplasia in approximately 75% of patients (Table 2; ninth column; 60–92%). Many patients with cortical dysplasia and normal MRIs are reported to have positive FDG-PET scans (Kim et al., 2000). In the UCLA series of 22 patients with normal or subtle MRI findings, 14 (64%) showed areas of hypometabolism on FDG-PET scans.

To increase the sensitivity of FDG-PET, the UCLA group recently modified the technique whereby pseudo-colored FDG-PET images representing escalating levels of hypometabolism were overlaid onto the structural MRI (Fig. 9) (Burri et al., 2008). This method identified cortical dysplasia in 98% of patients in the UCLA cohort, including a substantial proportion of patients with mild type I dysplasia with previously interpreted normal MRI scans (Table 4) (Salamon et al., 2008). Hence, FDG-PET can be a very useful tool in detecting cortical dysplasia in patients undergoing presurgical evaluation for their intractable epilepsy, especially if the MRI is normal or nonspecific for cortical dysplasia.

Ictal SPECT is another neuroimaging tool that has been applied to patients with probable cortical dysplasia (Gupta et al., 2004). Studies indicate that 57% of cortical dysplasia patients have localized ictal SPECT scans (Table 2; 10th column; 42–64%). Like FDG-PET, some patients with a normal MRI show positive ictal SPECT scans.

Areas of cortical dysplasia often produce abundant interictal discharges when sampled with intracranial EEG (Palmini et al., 1991; Ishibashi et al., 2002). Hence, magnetoencephalography (MEG)–magnetic source imaging (MEG-MSI) should be a valuable tool for identifying epileptogenic areas of cortical dysplasia by mapping areas that produce frequent interictal discharges (Fig. 7D). Although MEG-MSI has been available for several years, there are limited publications reporting the use of this technique in patients with cortical dysplasia. These studies report localized MEG-MSI scans in 97% (30 of 31) of patients with cortical dysplasia, and suggest that there may be differences in the distribution of spikes in patients with type I and type II disease (Otsubo et al., 1993; Morioka et al., 1999; Bast et al., 2004; Hader et al., 2004). This is similar to the initial UCLA experience, in which all 18 patients with cortical dysplasia sampled with MEG-MSI had positive localized studies prior to surgical resection (Fig. 7D). Therefore, MEG-MSI is likely a promising and underutilized technique that could improve the detection and localization of areas of cortical dysplasia in patients with refractory epilepsy. However, further studies are necessary to validate this technique in patients with cortical dysplasia (Knowlton et al., 2006; Wu et al., 2006).

Intracranial EEG

Because of the above-noted limitations of scalp EEG and MRI, patients with suspected cortical dysplasia are often implanted with intracranial electrodes to localize areas of ictal onset. The percentage of patients with

Table 6. MRI features of epilepsy surgery patients with cortical dysplasia

Study	Normal MRI, %	Thick GM, %	Blurring GW, %	Increased WM T2, %	Atrophy, %	Transmantle sign, %
Type I cortical dysplasia						
Krsek et al. (2008a); Miami (n = 79)	63	5	56	53	44	0
Krsek et al. (2008c); Germany (n = 24)	17	0	29	62	75	0
Tassi et al. (2002); (n = 37)	35	13	8	24	38	0
Kloss et al. (2002); (n = 26)	N/A	38	69	19	N/A	N/A
Kim et al. (2000); (n = 8)	87	12	12	12	N/A	N/A
Weighted average	37	11	42	41	48	0
Type II cortical dysplasia						
Krsek et al. (2008a); Miami (n = 51)	10	61	76	55	16	10
Krsek et al. (2008c); Germany (n = 16)	0	50	94	94	44	37
Tassi et al. (2002); (n = 15)	33	53	60	60	7	20
Cohen-Gadol et al. (2004) (n = 22)	9	82	N/A	55	N/A	68
Kloss et al. (2002); (n = 24)	N/A	54	67	62	N/A	N/A
Kim et al. (2000); (n = 11)	18	45	73	73	N/A	N/A
Weighted average	15	60	74	63	19	34
p-Value: Type I vs. Type II	<0.001	<0.001	<0.001	<0.01	0.001	<0.001

Thick GM, thickened gray matter; Blurring GW, blurring of the gray–white matter junction; Increased T2, Increased T2 signal in gray and white matter; Transmantle, transmantle dysplasia with signal going to the ventricle; N/A, not available from the study.

cortical dysplasia undergoing intracranial electrode procedures varies considerably from center to center. In published studies, 53% of patients with cortical dysplasia were reported to have intracranial electrode studies (Table 2; 11th column; 30–86%). In the ILAE survey, 36% of pediatric patients with cortical dysplasia had intracranial electrodes compared with 20% for children with other etiologies (Table 3). By comparison, in the UCLA cohort, intracranial electrodes were implanted in 6% of patients with cortical dysplasia (Table 4). Published studies do not report a difference in the use of intracranial electrodes in patients with mild type I (45%) compared with severe type II (47%) cortical dysplasia (Tassi et al., 2002; Widdess-Walsh et al., 2005; Krsek et al., 2008a,c). By comparison, in the UCLA cohort, more patients with type I (Table 4; 10%) had intracranial electrodes compared with those with type II cortical dysplasia (1%).

Once implanted, detection of ictal onset zones using intracranial electrodes is often not straightforward in patients with cortical dysplasia. Initial studies using electrocorticography described interictal "continuous epileptiform discharges" (CEDs) and fast frequency patterns as a hallmark for detecting areas of cortical dysplasia (Palmini et al., 1995; Gambardella et al., 1996; Whiting & Duchowny, 1999). Subsequent studies, however, found that these intracranial EEG findings were associated with nondysplastic etiologies (Guerreiro et al., 2003; Turkdogan et al., 2005). Likewise, in a recent study, 35% of ictal onsets were reported as diffuse, involving more than a dozen intracranial electrodes; in 42% of patients the ictal onsets were at more than one site with repeated seizures, and in 49% of cases the onsets were reported as being at the edge of the grid outside the region of electrode coverage (Widdess-Walsh et al., 2007). These findings indicate that the epileptogenic region is often deep or distant from the site of intracranial electrode placement. Likewise, another intracranial electrode study reported that areas of dysplasia that contained balloon cells (type IIB) were less likely to demonstrate ictal-onset EEG patterns compared with regions that contained dysmorphic–cytomegalic neurons without balloon cells (type IIA) (Boonyapisit et al., 2003). However, other reports indicate that complete removal of the cortical dysplasia lesion including areas containing balloon cells provides the best chance of seizure freedom after surgery (Kim et al., 2008; Krsek et al., 2008b; Mathern, 2008). Furthermore, the finding of postexcision spikes on intracranial EEG recordings does not predict whether patients will become seizure free after surgery (Krsek et al., 2008c). Hence, using intracranial electrodes, there are no specific interictal or ictal EEG signs that identify areas of cortical dysplasia, and ictal onsets are often ill-defined and diffuse or do not overlap with areas of severe dysplasia.

Coexistent Neuropathology

Cortical dysplasia has been associated with other brain pathologic changes that could be independent epileptogenic lesions. This is often referred to as "dual pathology," and includes the following main groups of substrates.

Tumors and infarcts with cortical dysplasia

Low-grade tumors are associated with seizures and may have regions adjacent to the lesion that on histopathology are very similar to areas of cortical dysplasia. The tissue contains disorganized cortex with large abnormal neurons

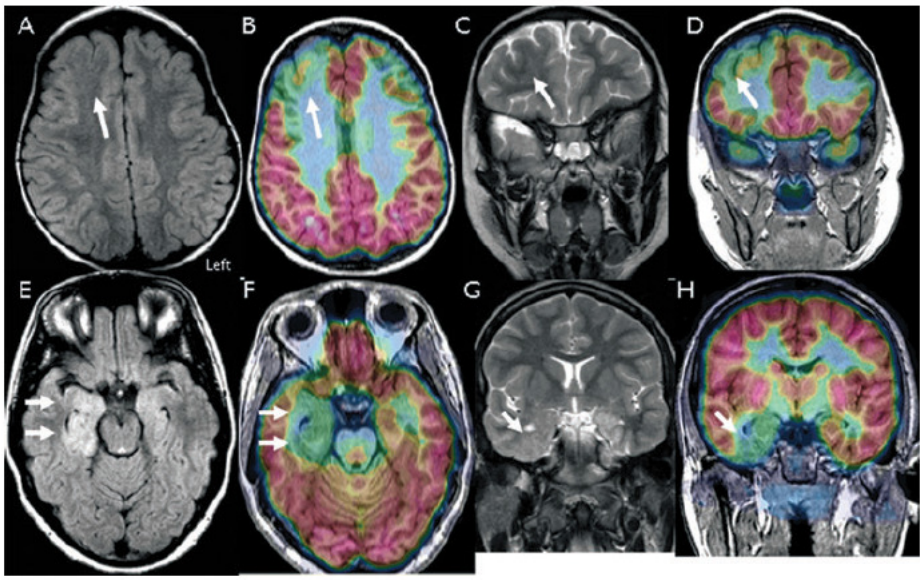

Figure 9.
Examples of 2-(^{18}F)Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) findings in patients with cortical dysplasia. (**A–D**) This 4-year-old began with seizures at 6 months of age and they occurred many per day. Scalp electroencephalography (EEG) showed interictal and ictal findings referable to the right frontal-temporal region. Axial fluid attenuated inversion recovery (FLAIR) (**A**) and coronal T2 magnetic resonance imaging (MRI) (**C**) images suggested an area of cortical dysplasia occupying the lateral surface of the right frontal lobe (arrows). FDG-PET overlaid onto the T1 MRI scans showed hypometabolism in a slightly larger region than the MRI abnormality (**B, D**; arrows). At surgery, electrocorticography (ECoG) showed background slowing and continuous spike discharges throughout the lateral, orbital-frontal, and mesial-frontal regions. Based on these findings, a right frontal resection was performed that included all tissue in front of the motor cortex including the mesial-frontal and orbital-frontal areas. Histopathology confirmed Palmini type IIA cortical dysplasia in all segments of the right frontal lobe including the orbital-frontal and mesial-frontal regions. This child is seizure free after surgery. (**E, F**) This 16-year-old began to experience seizures at age 12 years. At the time of surgery she was having multiple seizures per day. Scalp EEG localized interictal and ictal findings to a broad area of the right frontal, temporal, and parietal regions. MRI disclosed FLAIR changes in the right mesial temporal lobe including the hippocampus (**E**; arrows) and parahippocampal gyrus (**G**; arrow). FDG-PET images overlaid onto the MRI scan were concordant (**F, H**; arrows). A right temporal resection was performed. Histopathology showed Palmini type IIA cortical dysplasia without hippocampal sclerosis, and the patient has been seizure free since surgery.

on histopathology (Prayson & Frater, 2003). It is reported that cortical dysplasia is found in 4–20% of patients with DNET and gangliogliomas (Honavar et al., 1999; Widdess-Walsh et al., 2005; Park et al., 2006). It is unknown whether patients with low-grade tumors and cortical dysplasia have clinical characteristics that are different from those of patients with only low-grade tumors. Likewise, it is unclear whether dysplastic cortex contributes to seizure generation in patients with tumors. Similarly, 10% of patients with perinatal infarcts are reported to show cortical dysplasia on histopathology (Marin-Padilla et al., 2002; Prayson & Frater, 2003). More studies are needed to better define the clinical features of patients with cortical dysplasia and low grade tumors and infarcts.

Hippocampal sclerosis with cortical dysplasia

There is considerable controversy about whether hippocampal sclerosis is the "cause" or "result" of coexistent

mMCD and mild type I cortical dysplasia in a subgroup of patients with temporal lobe epilepsy. It has been proposed that hippocampal sclerosis can be the result of a "second-hit," whereby a preexisting structural abnormality (like abnormal temporal lobe cortical development) predisposes individuals to developing hippocampal sclerosis as a result of initial precipitating injuries (IPIs) (Raymond et al., 1995; Blumcke et al., 2002). Other studies have hypothesized that cortical disorganization and cerebral atrophy is an epiphenomenon from an early life IPI and not a developmental disorder or an independent epileptogenic lesion (Kasper et al., 1999; Mathern et al., 2002a, 2002b; Kalnins et al., 2004).

There is support for both of these concepts in the literature. For example, hippocampal sclerosis was reported in 20% of patients with cortical dysplasia in recent studies (Table 2; last column; 5–33%). Nearly all of these cases had mild type I cortical dysplasia or mMCD. A higher incidence of hippocampal sclerosis and mild cortical dysplasia is usually reported in adult compared with pediatric cohorts (Table 2) (Srikijvilaikul et al., 2003; Fauser et al., 2004; Krsek et al., 2008b). Furthermore, the incidence of IPIs is reported to be higher in patients with mild type I compared with severe type II cortical dysplasia (Fauser & Schulze-Bonhage, 2006; Krsek et al., 2008a,c).

Other clinicopathologic and neuroimaging studies report few if any meaningful clinical differences in patients with or without subtle cortical dysplasia and temporal lobe epilepsy from hippocampal sclerosis (Kasper et al., 2003; Mitchell et al., 2003; Diehl et al., 2004; Kalnins et al., 2004; Seidenberg et al., 2005; Adachi et al., 2006). Many patients with mMCD and mild type I cortical dysplasia and hippocampal sclerosis are reported to have smaller atrophic temporal lobes (Colombo et al., 2003; Bast et al., 2004; Andres et al., 2005; Chandra et al., 2007). Furthermore, in patients with dual pathology, ictal onsets using intracranial electrodes were reported to arise from the area of hippocampal sclerosis and not from the region of dysplasia (Fauser & Schulze-Bonhage, 2006). Likewise, most studies have reported minimal differences in becoming seizure free in patients who have or do not have mMCD and mild cortical dysplasia along with hippocampal sclerosis (Srikijvilaikul et al., 2003; Krsek et al., 2008a). Such findings raise doubts about whether subtle cortical lesions, like mMCD and type I cortical dysplasia, constitute independent epileptogenic foci in patients with hippocampal sclerosis and temporal lobe epilepsy, or if these lesions predispose a person to febrile seizures and IPIs.

Obviously, more carefully designed studies are necessary to discern what constitutes cortical dysplasia in patients with hippocampal sclerosis. In the future, it would be appropriate to separate patients with well-characterized mild and severe cortical dysplasia from those with mMCD and microdysgenesis in order to determine the incidence of hippocampal sclerosis with dysplasia. Likewise, future studies should determine if the presence or absence of temporal lobe encephalomalacia and cortical injury correlates with histopathologic criteria for cortical dysplasia with and without hippocampal sclerosis.

Surgical Procedures, Locations, and Outcomes

Types of surgery and their brain locations

As might be expected from the description of the characteristics of patients with mild and severe cortical dysplasia, there are differences in the type of surgical resections and in age at seizure onset and surgery (Leiphart et al., 2001). In published studies, 72% of patients with cortical dysplasia had focal or lobar resections, and the remaining had multilobar or hemisphere operations (Table 2; 14th column). Most of the focal lobar resections were in adult compared with pediatric cohorts (Table 2). In the ILAE survey of pediatric epilepsy surgery patients, 38% of patients with cortical dysplasia had hemispheric or multilobar resections, compared with 27% for other etiologies (Table 3). In the UCLA series, 37% of patients with cortical dysplasia had hemispheric or multilobar operations, and most of those patients had type II dysplasia (Table 4). In the published literature, 56% patients had type I cortical dysplasia (Table 2; 13th column). In adult cohorts, up to 80% of patients were reported to have type I cortical dysplasia (Kim et al., 2008). In the UCLA series, 66% of patients had type II cortical dysplasia, which is similar to studies of other younger cohorts (Table 4) (Salamon et al., 2008). Similarly, all lobes of the brain may be involved in patients with cortical dysplasia. However, more adult patients present with type I cortical dysplasia involving the temporal lobe compared with younger patients who present with type II dysplasia in extratemporal regions, including the frontal lobe (Table 4). This finding holds true even if patients with hippocampal sclerosis are excluded from the analysis. As demonstrated in several studies, including the UCLA series, there are no clinical differences based on gender or side of resection in patients with type I or type II cortical dysplasia (Table 4) (Tassi et al., 2002; Widdess-Walsh et al., 2005).

Postoperative seizure freedom

The percentage of patients who were seizure free after resective surgery for cortical dysplasia is generally favorable and nearly similar to patients undergoing epilepsy surgery for other etiologies (Spencer & Huh, 2008). In recent studies, 60% of patients are reported to be seizure free after surgery at last follow-up (Table 2; 15th column; 42–87%). In the UCLA series, 82% of patients were seizure free after surgery with 1–2 years of follow-up (Salamon et al., 2008). This is an improvement from studies published from 1971–1999, which reported that

38–40% of patients with cortical dysplasia were seizure free after surgery (Sisodiya, 2000). Of Taylor's initial report of patients with cortical dysplasia, 60% were seizure free after surgery (Taylor et al., 1971).

For cortical dysplasia patients, the most consistently reported predictor of seizure freedom is complete resection of the lesion. Complete resection is generally defined as removal of the lesion on neuroimaging or the interictal and ictal onset zones in patients undergoing intracranial electrode recordings. Based on these criteria, 30–35% of patients with cortical dysplasia have incomplete resection (Jayakar et al., 2008; Kim et al., 2008; Krsek et al., 2008a, 2008c). Patients with compete resection have a 77% chance of becoming seizure free, compared with 20% for those with incomplete resections (Table 7). The most frequently cited reason for incomplete resections is that areas of cortical dysplasia, often not visible on MRI, were located in cortical regions, the resection of which would lead to unacceptable motor, sensory, visual, or language deficits (Marusic et al., 2002). In cortical dysplasia patients with incomplete resections, seizure reoccurrence usually happens within 6 months of surgery (Mathern et al., 1999; Widdess-Walsh et al., 2007).

Other clinical variables reported to predict seizure freedom probably interplay with incomplete resection of the cortical dysplasia lesion. Some studies have reported that fewer patients with type I cortical dysplasia are seizure free when compared with those with type II dysplasia (Tassi et al., 2002; Chung et al., 2005; Fauser et al., 2008; Kim et al., 2008). Other studies have reported more favorable outcomes for patients with mild type I cortical dysplasia, although a significant proportion of these patients also had hippocampal sclerosis (Fauser et al., 2004). Hence, it would be helpful if future studies reported outcomes in patients with mild and severe cortical dysplasia without dual pathology. Likewise, an extratemporal location, ill-defined ictal EEG onsets, secondary generalized tonic–clonic seizures, use of intracranial electrodes, and large resections were reported to correlate with poor seizure control after surgery (Hudgins et al., 2005; Widdess-Walsh et al., 2005; Alexandre et al., 2006; Park et al., 2006; Kral et al., 2007; Kim et al., 2008). These correlations probably relate to the difficulty in imaging mild type I cortical dysplasia, especially in extratemporal locations. Of note, a few mostly adult studies have reported that shorter seizure durations correlated with a higher chance of becoming seizure free after surgery (Fountas et al., 2004; Siegel et al., 2006; Fauser et al., 2008). This finding has not been replicated in pediatric patients with cortical dysplasia (Krsek et al., 2008a).

Table 7. Percentage of patients with cortical dysplasia seizure free based on complete or incomplete resection of MRI and EEG focus

Study	Complete resection	Incomplete resection
Kloss et al. (2002)	80% (21/26)	17% (5/30)
Kim et al. (2008)	82% (77/94)	30% (17/56)
Krsek et al. (2008b)	70% (72/103)	22% (10/96)
Alexandre et al. (2006)	86% (12/14)	50% (9/18)
Weighted average	77% (182/237)	20% (41/200)

Chi-square: $p < 0.0001$.

Studies of long-term seizure control after surgery in patients with cortical dysplasia report variable results. Some studies with mostly mild type I cortical dysplasia, including a proportion of patients with hippocampal sclerosis, report stable or increased rates of becoming seizure free, four or more years after surgery (Kloss et al., 2002; Hamiwka et al., 2005; Krsek et al., 2008a). Other studies with mostly severe type II cortical dysplasia and type I without hippocampal sclerosis have shown that 15–17% of patients who were seizure free 2 years after surgery have reoccurrence of seizures three or more years after the operation (Mathern et al., 1999; Kral et al., 2007; Widdess-Walsh et al., 2007). More studies on larger uniformly defined cohorts are necessary to judge if patients remain seizure free many years after surgery, and whether there are differences in patients with mild and severe cortical dysplasia.

Antiepilepsy medications

The number of patients with cortical dysplasia off medications after surgery varies from study to study. In the published literature, from 14–41% of patients with cortical dysplasia were reported as not taking antiepilepsy drugs 1–2 years after surgery (Kral et al., 2007; Krsek et al., 2008b). In the UCLA series, 22% of patients with cortical dysplasia were not taking medications 2 years after surgery. In the UCLA cohort, there were no differences in the percentage of patients off medications for those with mild or severe cortical dysplasia.

Complications and reoperations

Morbidity and mortality are generally low in patients undergoing surgery for cortical dysplasia. In published studies since 2002, one death (0.2%) was reported (Alexandre et al., 2006). Transient and permanent complications were reported in 13% of patients, of which 11% resolved within 3 months of surgery leaving a permanent complication rate of 2% (Table 2; 12th column). Most transient complications include increased mild neurologic deficits and infections. Permanent complications include new neurologic deficits and acquired hydrocephalus. In the contemporary UCLA series, no deaths were reported, 22% had transient complications that resolved within 3 months of surgery, and permanent complication rate was 2%, consisting of patients that required cerebrospinal

fluid (CSF) shunts (Jahan et al., 1997). There are no reported differences in surgical complications in patients with type I and type II cortical dysplasia.

With a 30% chance of an incomplete resection, it is not surprising that many patients with cortical dysplasia undergo repeat surgery. In published studies, 14% of patients with cortical dysplasia undergo a reoperation for failure of seizure control after a first surgery (range 13–15%) (Kloss et al., 2002; Krsek et al., 2008a, 2008c). In the UCLA series, 5% of patients with cortical dysplasia had reoperations. The success rate with repeat surgery has not been consistently reported (Siegel et al., 2005). In one series, 4 of 6 patients (66%) became seizure free after reoperation (Krsek et al., 2008c). In the UCLA series, 2 of 4 patients (50%) with cortical dysplasia were seizure free after a second operation. To date, studies have not reported if the rate of reoperation is different in patients with mild or severe cortical dysplasia.

Neuropsychologic outcomes

Developmental assessments before surgery indicate that 33–68% of patients with cortical dysplasia have reduced intelligence scores. However, the results have been inconsistent as to whether patients with type I or type II cortical dysplasia have worse presurgical neuropsychological assessments. Studies have reported that patients with type I dysplasia have worse intelligence scores than those with type II dysplasia (Tassi et al., 2002; Krsek et al., 2008c). Other studies report that patients with type II dysplasia are worse than those with type I, or that there are no differences in intelligence scores based on histopathologic grade (Klein et al., 2000; Widdess-Walsh et al., 2005; Park et al., 2006; Krsek et al., 2008a). It is important to note that the size of the lesion is probably another factor to consider in assessing intelligence scores in patients with cortical dysplasia. In one study, more children with extensive cortical dysplasia on neuroimaging were reported to show severe mental retardation compared with those with focal cortical dysplasia (Klein et al., 2000). Another study reported a higher frequency of maladaptive behavioral disorders in patients with mild compared with severe cortical dysplasia, but no differences were found in the incidence of attention deficit hyperactivity disorder and disorders of speech and language (Krsek et al., 2008c). Hence, more comprehensive studies are needed to explain the variability in neuropsychological profiles in patients with mild and severe cortical dysplasia that may depend on duration of epilepsy, age at seizure onset, and extent of disease on neuroimaging. Of note, there are preliminary data supporting the notion that with early surgery and seizure freedom, children with cortical dysplasia may have improved developmental scales, and this depends on stopping the seizures within 2 years of onset (Jonas et al., 2004, 2005). It is unclear if early surgery is beneficial in adult patients with cortical dysplasia presenting with new-onset epilepsy.

Pathogenesis and Epileptogenesis of Cortical Dysplasia

Potential mechanisms of pathogenesis that explain epileptogenesis are beginning to emerge from studies of tissue removed at surgery from patients with cortical dysplasia. The findings from these studies have not always been consistent, and this may depend in part on the age of the patients and whether they have mild type I or severe type II cortical dysplasia. Initially, it was thought that mechanisms of epileptogenesis might involve an increase in AMPA and NMDA–receptor mediated cellular excitation or a loss of GABA-containing neurons leading to reduced cellular inhibition (Spreafico et al., 1998; Kerfoot et al., 1999; Najm et al., 2000; Alonso-Nanclares et al., 2005). However, these ideas were probably overly simplistic as they did not take into account developmental changes in cellular receptors and circuits in dysplastic tissue (Andre et al., 2004; Avoli et al., 2005).

Recently, most investigators have focused on how abnormal cortical development can induce or contribute to epileptogenesis in cortical dysplasia tissue (Najm et al., 2007). Recent morphologic and in vitro electrophysiologic studies support the notion that areas of severe type II cortical dysplasia involve a more significant and earlier failure of cortical development than mild type I dysplasia (Andre et al., 2004; Cepeda et al., 2006; Andre et al., 2007, 2008). If correct, then seizure generation has been hypothesized to be the consequence of incomplete cellular maturation, and pathogenetic mechanisms will likely vary in mild and severe cortical dysplasia tissue. These research endeavors are still in their infancy; more studies are needed to understand possible mechanisms of epileptogenesis in cortical dysplasia tissue, and if the mechanisms are different in cases of mild compared with severe disease.

Critical Review and Future Challenges

From this literature review, the 2004 ILAE survey, and the UCLA cohort, a picture emerges of the clinical characteristics of patients with cortical dysplasia and the features that distinguish those with mild Palmini type I from severe Palmini type II cortical dysplasia. The most consistent findings are summarized in Table 8, and begin to describe what may become unique epilepsy surgery syndromes involving patients with cortical dysplasia. Although we have learned a great deal over the last decade from retrospective surveys of surgical cohorts, our knowledge

Table 8. Summary of clinical characteristics of patients with cortical dysplasia

All patients with cortical dysplasia
Constitutes the most frequent histopathology in children and the second or third most common etiology in adults
Typically present with seizures and have surgery at an earlier age than other etiologies in epilepsy surgery patients
Most epilepsy surgical cases less than 3 years of age involve cortical dysplasia
About 15% of cases with cortical dysplasia will present with status epilepticus, and 30% with a history of infantile spasms
About 50% of patients with cortical dysplasia will present with localizing interictal and 68% with localized ictal scalp EEG findings
MRI is abnormal with signs specific for cortical dysplasia in about 65% of cases
FDG-PET is positive in approximately 75–90% of patients with cortical dysplasia. Ictal SPECT is positive in slightly over 50% of cases
Overall, 60% are seizure free after surgery. About 80% of patients with complete resection are seizure free compared with 20% with incomplete resections
Mild type I vs. severe type II cortical dysplasia
In children, about half of patients will have mild cortical dysplasia. In adults, the majority have mild cortical dysplasia
Patients with severe cortical dysplasia are generally younger at age at surgery, age at seizure onset, have shorter seizure duration, and higher seizure frequencies than mild type I cases
Severe type II cortical dysplasia is most often extratemporal or hemispheric while mild Type I dysplasia is most often temporal and lobar/focal
Approximately 90–100% of patients with type II dysplasia will show MRI abnormalities compared with 15–60% of patients with type I cortical dysplasia
There is a suggestion that about 15% of patients with type II cortical dysplasia may relapse with seizure many years after surgery
Size of cortical dysplasia based on neuroimaging
Hemispherectomy/multilobar cases are generally younger at age at surgery, age at seizure onset, and have shorter seizure duration than lobar/focal cases for patients with both mild and severe cortical dysplasia

of the clinical, electrographic, neuroimaging, and histopathologic elements of patients with cortical dysplasia should be considered rudimentary and incomplete. Future studies would benefit from prospective multicenter collaborations that test current assumptions and ideas about the pathogenesis of cortical dysplasia and how this tissue generates seizures. A list of pertinent questions that could form the focus of the next generation of research investigations is indicated in the following.

Are we using the best histopathologic classification system to define cortical dysplasia? Do patients form distinct subgroups, or is there a continuous spectrum of histopathologic abnormalities of altered cortical development that defines patients with cortical dysplasia and correlates with clinical features of their epilepsy?

For clinical and basic researchers, the introduction of the Palmini classification system was an important step to uniformly define the nomenclature and grading of patients with cortical dysplasia. Furthermore, as illustrated in this review, there are some clinical and neuroimaging differences found when comparing patients with mild type I with severe type II cortical dysplasia. However, most of the reported differences in patients with type I and type II cortical dysplasia involve age at presentation, seizure frequency, and neuroimaging with minimal or no differences in seizure semiology, interictal and ictal EEG, and other findings. In addition, the Palmini grading system has shown few substantial and consistently reported differences comparing patients with type IA with type IB and patients with type IIA with type IIB cortical dysplasia (Table 1) (Boonyapisit et al., 2003; Lawson et al., 2005; Widdess-Walsh et al., 2005; Krsek et al., 2008a). Hence, it appears that there are inherent limitations to the Palmini system. In other words, results using the Palmini classification system are similar to earlier schemes that separated patients into those with mild and severe cortical dysplasia based on histopathologic criteria (Mischel et al., 1995; Tassi et al., 2002).

The Palmini scale relies as major criteria on the presence or absence of dysmorphic–cytomegalic neurons and balloon cells and does not take into consideration other histopathologic features of abnormal cortical development. Likewise, the Palmini scale does not consider the potential value of quantitative morphometric techniques and immunohistochemical staining in classifying patients with cortical dysplasia (Kerfoot et al., 1999; Andres et al., 2005). Hence, future investigations may wish to determine if patients with cortical dysplasia fit into clearly definable histopathologic subgroups, or does the histopathology follow a continuous spectrum of cytologic and histologic abnormalities. Preliminary analysis of the UCLA series suggests that a continuous histopathologic classification system might be better suited for epilepsy surgery patients with cortical dysplasia (Fig. 10A). In this figure, the frequency of patients with increasing histopathologic elements of abnormal cortical development is plotted. Most patients have two to five features consistent with cortical dysplasia. Furthermore, the distribution overlaps between patients with mild type I and severe type II cortical dysplasia using the Palmini system (Fig. 10B). By using more histopathologic characteristics of abnormal cortical development in a classification system it may be possible to develop a grading system that better captures the broad clinical characteristics of patients with cortical dysplasia. Such a system might also address if mMCD and microdysgenesis can be uniformly and clearly defined and readily distinguished from milder forms of cortical dysplasia.

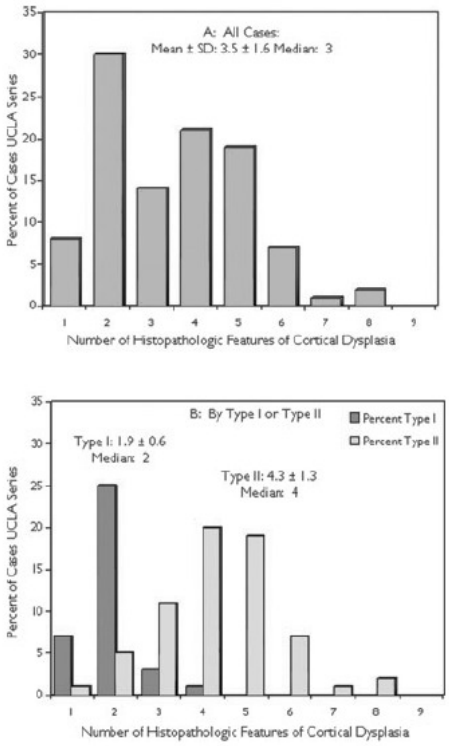

Figure 10.
Frequency histograms showing the percentage of cases from the 2000–2007 UCLA cohort with one or more histopathologic features of abnormal cortical development consistent with cortical dysplasia. Cases were reviewed for the presence of: (1) cortical disorganization and dyslamination; (2) excessive heterotopic white matter neurons; (3) dysmorphic–cytomegalic neurons; (4) balloon cells; (5) excessive heterotopic neurons in the cortical molecular layer; (6) marginal and nodular glioneuronal heterotopias; (7) polymicrogyria; (8) immature neurons; and (9) persistence of the subpial granular cell layer. (**A**) The top graph shows the distribution of all patients with cortical dysplasia. Notice the continuum between patients with 1–8 histopathologic features of abnormal cortical development. (**B**) Distribution for patients with Palmini type I (orange bars) and Palmini type II (yellow bars) cortical dysplasia. Notice the overlap for both patient groups if the patient had one to four histopathologic features of cortical dysplasia.

Should a classification system of patients with cortical dysplasia take into account the size of the lesion on neuroimaging?

In this review, we showed that there were clinical differences comparing patients with mild and severe cortical dysplasia. We also showed that age at seizure onset, age at surgery, and seizure frequency correlated independently with the size of the lesion on MRI (Fig. 5). This raises the question of whether a comprehensive classification system for patients with cortical dysplasia should incorporate neuroimaging characteristics into the scheme. Neuroimaging features can be assessed noninvasively and quantitatively (Andres et al., 2005; Barkovich et al., 2005). This might include size (Fig. 5) along with specific MRI features such as thickened gray matter and the transmantle sign (Table 6, Fig. 6). Whatever the features, any neuroimaging classification system should identify areas of cortical dysplasia in patients undergoing presurgical evaluations, and predict the histopathologic grade of the lesion.

Are there different etiologies in patients with milder forms of cortical dysplasia?

There is considerable confusion about the presence or absence of abnormalities of cortical development if the MRI is normal or shows encephalomalacia in patients with mild cortical dysplasia. Therefore, it would be important for future studies to address whether the histopathologic features in patients with mMCD and mild cortical dysplasia are different depending on MRI features. It would also be important to discern whether the histopathologic characteristics of mMCD and mild cortical dysplasia are different in patients with temporal lobe epilepsy with and without hippocampal sclerosis and in patients with other dual pathologies such as perinatal strokes (Marin-Padilla, 1999; Marin-Padilla et al., 2002).

What is the incidence of cortical dysplasia in patients with refractory epilepsy?

A substantial proportion of patients with cortical dysplasia have nonlocalizing foci using scalp EEG and "normal" MRI scans. Many of these are adult patients with mild cortical dysplasia. This raises the important question: How many patients with cortical dysplasia are we missing by using current noninvasive presurgical protocols that rely heavily on positive structural MRI scans? The answer could be a substantial number. Hence, an important challenge will be to validate "newer" presurgical protocols and technologies that can noninvasively screen patients with refractory epilepsy for the presence of subtle cortical dysplasia and improve our accuracy in identifying patients with this disorder. This will be

especially important for patients with mild cortical dysplasia without coexistent hippocampal sclerosis that are currently MRI negative.

Several older and newer structural and functional neuroimaging techniques are candidate tools that might increase detection of cortical dysplasia in refractory epilepsy patients (Hwang et al., 2001; Akhtari et al., 2006). For MRI, these techniques might include magnetic resonance spectroscopy (MRS) using high (>3T) field strength magnets, diffusion tensor imaging (DTI), dynamic perfusion imaging, functional MRI, and structural image analysis to quantify areas of gray and white matter abnormalities (Eriksson et al., 2001; Raybaud et al., 2006; Widjaja et al., 2007). Newer PET ligands, such as flumazenil and alpha-(^{11}C)methyl-L-tryptophan, need to be tested in patients with mild and severe cortical dysplasia, and new PET ligands developed perhaps based on findings from studies of excised cortical dysplasia tissue (Juhasz et al., 2000a, 2000b). Newer methods of EEG source imaging with high density scalp electrodes need to be studied in patients with mild and severe cortical dysplasia (Sperli et al., 2006).

Are there different long-term surgical outcomes for patients with mild and severe cortical dysplasia?

At present, there appear to be minimal differences in the percentage of patient's seizure free 1–2 years after surgery, if the area of cortical dysplasia is completely removed. However, it is unclear if patients remain seizure free four or more years after surgery, and if outcomes vary depending on whether they had mild or severe cortical dysplasia. Hence, long-term studies of outcomes are needed to determine if there are differences in the percentage of patients who are seizure free along with developmental and psychosocial results for patients with mild and severe cortical dysplasia. These studies should exclude patients with dual pathology, such as hippocampal sclerosis, who are known to be capable of independent epileptogenesis, so that uniform populations of patients with cortical dysplasia are studied.

Is there a developmental explanation for the greater number of patients with mild cortical dysplasia who have lesions in the temporal lobe relative to those with severe dysplasia with lesions in extratemporal locations?

If cortical dysplasia represents a malformation of cortical development, then understanding why different lobes of the brain are involved with mild and severe dysplasia may offer clues to the pathogenesis of this disorder. Understanding pathogenesis might predict mechanisms of epileptogenesis that would be useful to develop into treatments.

What are the mechanisms of epileptogenesis in cortical dysplasia tissue? Do mechanisms differ in patients with mild and severe cortical dysplasia? Can mechanisms gleaned from basic science research be developed into novel treatments for patients with cortical dysplasia?

A current frustration for clinical teams that treat patients with cortical dysplasia is the realization that a substantial number of patients cannot undergo complete resection of the MRI lesion or EEG focus because it involves areas of important functional cortex. Another future challenge will be to develop novel therapies that might control seizures so that more patients with cortical dysplasia can be successfully treated without increasing the risk of new neurologic deficits. This may involve nonsurgical remedies developed on the basis of mechanisms learned from the basic science laboratory, involving abnormal cells and circuits in cortical dysplasia tissue. These therapies will also need to include emerging knowledge of the genetic abnormalities that may be different in patients with mild and severe cortical dysplasia (Ljungberg et al., 2006). Hence, there is a need for more resources devoted to understanding the mechanisms of epileptogenesis and pathogenesis along with genetics in patients with cortical dysplasia, and whether these mechanisms are different in those with mild and severe disease. The use of human tissue also offers the unique opportunity to try new pharmacologic treatments as an adjunct in therapy discovery for patients with cortical dysplasia. Therefore, it is anticipated that in the future we will understand more about the clinical characteristics and mechanisms of epileptogenesis in patients with mild and severe cortical dysplasia, which can be translated into novel therapies that may be targeted to the distinct histopathologic elements found in this malformation of cortical development.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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ANEXO B - ARTIGO PUBLICADO NA REVISTA NEUROLOGY

Improved outcomes in pediatric epilepsy surgery

The UCLA experience, 1986–2008

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ABSTRACT

Objective: Epilepsy neurosurgery is a treatment option for children with refractory epilepsy. Our aim was to determine if outcomes improved over time.

Methods: Pediatric epilepsy surgery patients operated in the first 11 years (1986–1997; pre-1997) were compared with the second 11 years (1998–2008; post-1997) for differences in presurgical and postsurgical variables.

Results: Despite similarities in seizure frequency, age at seizure onset, and age at surgery, the post-1997 series had more lobar/focal and fewer multilobar resections, and more patients with tuberous sclerosis complex and fewer cases of nonspecific gliosis compared with the pre-1997 group. Fewer cases had intracranial EEG studies in the post-1997 (0.8%) compared with the pre-1997 group (9%). Compared with the pre-1997 group, the post-1997 series had more seizure-free patients at 0.5 (83%, +16%), 1 (81%, +18%), 2 (77%, +19%), and 5 (74%, +29%) years, and more seizure-free patients were on medications at 0.5 (97%, +6%), 1 (88%, +9%), and 2 (76%, +29%), but not 5 (64%, +8%) years after surgery. There were fewer complications and reoperations in the post-1997 series compared with the pre-1997 group. Logistic regression identified post-1997 series and less aggressive medication withdrawal as the main predictors of becoming seizure-free 2 years after surgery.

Conclusions: Improved technology and surgical procedures along with changes in clinical practice were likely factors linked with enhanced and sustained seizure-free outcomes in the post-1997 series. These findings support the general concept that clearer identification of lesions and complete resection are linked with better outcomes in pediatric epilepsy surgery patients. ***Neurology***® **2010;74:1768–1775**

GLOSSARY

AED = antiepileptic drug; **FDG** = fluorodeoxyglucose; **HIPAA** = Health Insurance Portability and Accountability Act; **IRB** = institutional review board; **SEGA** = subependymal giant cell astrocytoma; **TSC** = tuberous sclerosis complex; **UCLA** = University of California, Los Angeles.

Surgery for children with refractory epilepsy has become an important treatment option over the past 30 years. Initially, most patients were adolescents with focal lesions involving the temporal lobe similar to adult epilepsy surgery.[1,2] With modern neuroimaging (e.g., MRI SPECT and fluorodeoxyglucose [FDG]–PET), the number of surgical centers expanded, as did etiologies and types of operations. Today, pediatric epilepsy surgery has evolved to include extratemporal operations and cerebral hemispherectomy for children of all ages. Etiologies range from cortical dysplasia, tumors, and perinatal strokes to rarer syndromes such as hemimegalencephaly, tuberous sclerosis complex (TSC), Rasmussen encephalitis, Sturge-Weber syndrome, and hypothalamic hamartomas.[3] Many children are treated because they are at risk for epileptic encephalopathies.[4]

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Table 1 Characteristics of University of California, Los Angeles pediatric epilepsy surgery cohorts pre- and post-1997

Variable	All years (n = 571)	Pre-1997 (n = 192)	Post-1997 (n = 379)	p Value pre- vs post-1997
Total cases/y, mean ± SD	25.2 ± 13.1	16.5 ± 8.7	34.7 ± 10.3	0.0002[a]
Resection cases/y, mean ± SD	18.4 ± 8.5	14.4 ± 7.3	22.7 ± 7.9	0.016[a]
Palliative cases/y, mean ± SD	6.3 ± 5.9	1.7 ± 1.4	11.4 ± 4.6	<0.0001[a]
Resection cases as % of all surgeries	74%	90%	67%	<0.0001[a]
Types of palliative cases, n				
Corpus callosotomy	27	20	7	<0.0001[a]
Vagus nerve stimulator	119	0	119	

[a] Significant difference ($p < 0.05$). Statistical tests include t tests and χ^2 where appropriate.

Studies report favorable outcomes on surgical cohorts from single centers, groups of centers focused for an age category, and patients with similar etiologies and procedures.[3,5-13] The aim of this study was to determine if outcomes improved over time.

METHODS Patient cohorts. The initial cohort consisted of all patients who underwent epilepsy neurosurgery at the UCLA Pediatric Epilepsy Surgery Program from January 1986 to December 2008 (n = 580). Patients had pharmacoresistant epilepsy, defined as persistent unprovoked seizures after adequate trials of 2 or more antiepileptic drugs (AED).[14] Excluded were patients who had craniotomy without cortical resection (biopsy only; n = 4), diagnostic intracranial electrodes without resection (n = 4), and multiple subpial transections without cortical excision (n = 1), leaving a final cohort of 571.

Study design. Patients were separated into 2 groups based on the date of surgery. The pre-1997 group were patients operated from January 1986 to December 1997 (n = 192). The post-1997 group included patients operated from January 1998 to December 2008 (n = 379). The 1997 to 1998 transition was chosen because it was the midpoint of the series and a previous publication summarized our epilepsy surgical experience from that era.[6] The findings of that study altered our approach in the post-1997 period. Specifically, we strove to use multimodality neuroimaging to enhance identification of epileptogenic lesions, advocated for complete surgical resection of the lesion, and altered postsurgical medication management. Patients were further subclassified by their operative procedure into those undergoing palliative (corpus callosotomy and vagus nerve stimulators; n = 146) and resection operations (n = 425). Additional details are available in e-Methods on the *Neurology*® Web site at www.neurology.org.

Standard protocol approvals, registrations, and patient consents. This research was approved by the University of California, Los Angeles (UCLA) institutional review board (IRB), and since enactment of Health Insurance Portability and Accountability Act (HIPAA), patients or families have signed research informed consents and HIPAA authorizations. Prior to enactment of HIPAA, this study was considered by UCLA's IRB to be exempt from requiring research informed consent. This study is not a clinical trial, and it is not registered in any public registry.

Statistical analyses. The pre-1997 and post-1997 groups were compared for differences in clinical variables, surgical procedures, and postsurgical outcomes. StatView 5 (SAS Institute, Inc., Cary, NC) was used for statistical analysis. Univariate statistical tests included Student *t* test, analysis of variance, and χ^2. Multivariate tests included logistic regression and log-linear analysis. All tests were 2-tailed and the threshold for significance was set a priori at $p < 0.05$. Univariate statistical analysis did not include adjustments for multiple comparisons.

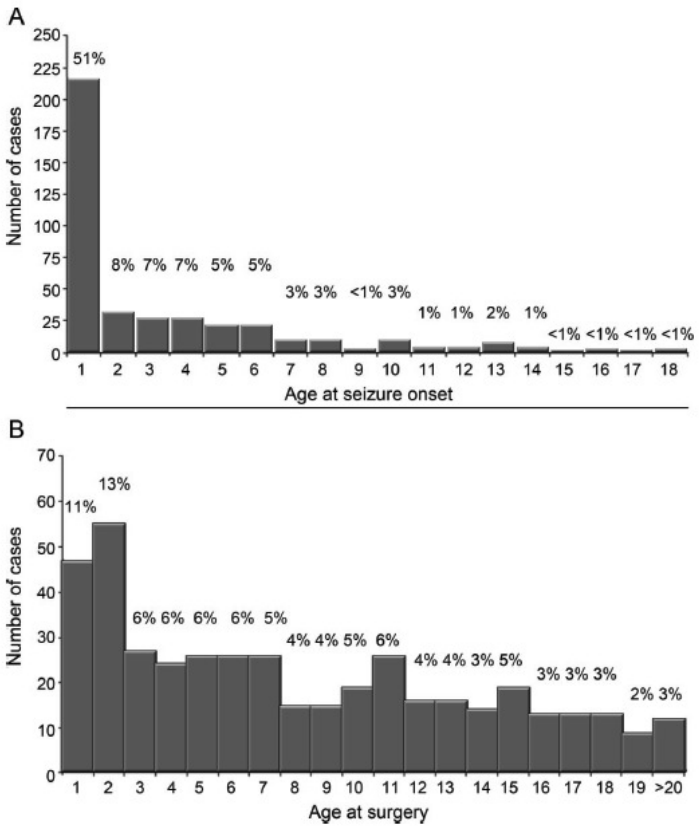
RESULTS General comparisons. The average cases per year and the proportion of palliative operations increased in the post-1997 series compared with the pre-1997 group (table 1). For the post-1997 series, there was a 58% increase in resection and a 570% increase in palliative cases per year ($p < 0.016$) compared with the pre-1997 group. In the pre-1997 group, palliative operations were 10% of all pediatric epilepsy surgery procedures, and consisted of corpus callosotomy. In the post-1997 series, palliative operations were 33% of all surgical cases, and fewer corpus callosotomy procedures were performed. Vagus nerve stimulation, which was approved by the Food and Drug Administration in 1997, comprised 90% (119/126) of palliative procedures in the post-1997 series.

Comparisons of resection cases. For UCLA pediatric patients undergoing resections, age at seizure onset was 1 year or less in 51% of cases, which is similar to findings from other pediatric epilepsy surgical centers (figure, A).[3] However, 24% of resection patients had their operation by age 2 years, which is younger than reported by many centers (figure, B).

There were no differences in most presurgical clinical characteristics comparing the pre- and post-1997 groups (table 2). Age at seizure onset, age at surgery, epilepsy duration, gender, side of resection, percentage of patients with a history of infantile spasms, and the percentage of patients with daily or more seizures were similar comparing the pre- with the post-1997 group (table 2; $p > 0.12$). Overall, 80% of patients underwent hemispherectomy or extratemporal operations compared with 20% with temporal lobe resections, which is greater than reported from many pediatric epilepsy surgery centers.[3,7,8,11] There were no differences in the ratio of temporal vs extratemporal operations comparing the pre- and post-1997 groups ($p = 0.377$).

Within the UCLA cohort, differences were noted in types of operations, etiologies, and use of intracranial electrodes comparing the pre- and post-1997 groups. Compared with the pre-1997 group, patients in the post-1997 series had proportionally more lobar/focal (+11%; $p = 0.001$; log-linear analysis) and fewer multilobar resections (−15%; table 2; $p = 0.002$). Using log-linear analysis, there was a higher proportion of patients with TSC (+7%; $p = 0.024$),

Figure **Frequency histogram**



Age at seizure onset (A) and age at surgery (B) for resection cases from 1986 to 2008 for University of California, Los Angeles's pediatric epilepsy surgery patients. Percentages are shown above each bar.

and fewer cases of nonspecific gliosis (−7%; $p = 0.002$) in the post-1997 compared with pre-1997 groups. Other etiologies were not different between the 2 series ($p > 0.05$). Overall, diagnostic intracranial EEG studies (phase II) were performed in 4% of UCLA pediatric epilepsy surgery patients (table 2). Intracranial electrodes were used in 15 patients in the pre-1997 group, compared with 2 patients in the post-1997 series ($p = 0.0005$).

Seizure freedom after resection. The percentage of patients with outcome data (reporting rate) decreased with longer follow-up durations for both the pre-1997 and post-1997 groups (table 3). Compared with the pre-1997 group, the post-1997 series had better reporting rates at 0.5 and 1 year ($p < 0.012$), and similar reporting rates at 2 and 5 years after surgery ($p > 0.21$).

The percentage of patients seizure-free was greater in the post-1997 series compared with the pre-1997 group at 0.5 (+16%), 1 (+18%), 2 (+19%), and 5 (+29%) years after surgery ($p < 0.0003$). In the pre-1997 group, the percentage of patients seizure-free decreased from 67% at 0.5 years to 45% at 5 years after surgery (−22%; $p = 0.0014$). In the post-1997 series, the percentage of patients seizure-free was 83% at 0.5 years that decreased to 74% at 5 years after surgery (−9%; $p = 0.207$).

There was less variability in seizure category in the post-1997 series. In patients with at least 2 years of follow-up, more patients were always seizure-free (+31%), fewer patients were never seizure-free (−21%) or had late recurrence of seizures (−7%) in the post-1997 series compared with the pre-1997 group ($p < 0.0001$). Likewise, more patients became seizure-

Table 2 Characteristics of resection cases, University of California, Los Angeles pediatric series pre- and post-1997

Variable	All years (n = 425)	Pre-1997 (n = 172)	Post-1997 (n = 253)	p Value
Age at seizure onset, y, mean ± SD	2.8 ± 3.8	2.3 ± 3.2	2.7 ± 3.4	0.217
Age at surgery, y, mean ± SD	7.7 ± 6.3	7.2 ± 6.2	8.1 ± 6.3	0.122
Epilepsy duration, y, mean ± SD	4.9 ± 4.6	4.8 ± 4.7	4.9 ± 4.5	0.747
Female, %	46	44	47	0.618
Left side, %	52	52	52	0.897
History of infantile spasms, %	30	32	29	0.181
Daily or greater seizure frequency, %	78	83	74	0.161
Intracranial electrodes, %	4	9	<1	0.0005[a]
Operative location, %				0.377
Hemispheric	42	39	43	
Extratemporal	38	42	35	
Temporal	20	19	22	
Operation type, %				<0.0001[a]
Hemispherectomy	42	39	43	
Multilobar	15	24[a]	9[a]	
Lobar/focal	43	37[a]	48[a]	
Histopathology/etiology, %				0.0030[a]
Cortical dysplasia	36	34	37	
Atrophy/ischemia/infection	18	22	15	
Tumor	8	7	9	
Hippocampal sclerosis	8	8	9	
Hemimegalencephaly	8	7	8	
Rasmussen syndrome	8	8	7	
Tuberous sclerosis complex	7	3[a]	10[a]	
Nonspecific gliosis	5	9[a]	2[a]	
Sturge-Weber syndrome	2	3	1	
Vascular	<1	<1	0	

[a] Difference by subgroup using log-linear analysis ($p < 0.05$; see text).

free after initial failure after surgery in the post-1997 series compared with the pre-1997 group (+4%).

The percentage of patients seizure-free 2 years after surgery was different by location, type of operation, and etiology (table 3). For all patients, those who had nonhemispheric extratemporal operations were less likely to be seizure-free (56%) compared with cases undergoing hemispherectomy (75%) and temporal (79%) resections ($p = 0.0006$). Similarly, patients who had multilobar operations were less likely to be seizure-free (55%) compared with patients undergoing hemispherectomy and lobar/focal (67%) resections ($p = 0.024$). By etiology, more patients with hippocampal sclerosis and tumors were seizure-free compared with those with hemimegalencephaly, Rasmussen syndrome, and TSC ($p = 0.0054$). Compared with the pre-1997 group, the post-1997 series showed that more patients were seizure-free who had hemispherectomy, extratemporal resections, and lobar/focal operations ($p < 0.041$), but not temporal or multilobar resections ($p > 0.07$). Likewise, compared with the pre-1997 group, the post-1997 series had a higher percentage of patients seizure-free with hemimegalencephaly ($p < 0.0001$) and TSC ($p = 0.028$). Other etiologies showed no differences in seizure-free outcomes comparing the pre- with the post-1997 groups.

Using outcomes at 2 years postsurgery, the percentage of patients seizure-free for both the pre- and post-1997 groups did not correlate with age at seizure onset ($p = 0.93$), age at surgery ($p = 0.61$), epilepsy duration ($p = 0.62$), gender ($p = 0.69$), side of resection ($p = 0.66$), history of infantile spasms ($p = 0.80$), and presurgery seizure frequency ($p = 0.48$).

AEDs after surgery. Medication use after surgery was different comparing the pre- and post-1997 groups (table 4). Although all patients met criteria for medically refractory epilepsy, 5 patients (1%) were not using AEDs at the time of surgery (parent preference).

Overall, the number of AEDs per patient decreased at all time points after surgery (table 4). The proportion of patients using AEDs decreased from 96% at 0.5 year to 77% at 5 years after surgery (table 4). The withdrawal of AEDs was faster in the pre-1997 group, with 31% not taking AEDs at 2 years of follow-up, compared with 15% of patients in the post-1997 series ($p = 0.0005$).

Similar findings were seen in the use of AEDs in seizure-free patients after surgery. Compared with the pre-1997 group, the post-1997 series had more seizure-free patients taking AEDs at 0.5 (97%; +6%), 1 (88%; +9%), and 2 (76%; +29%), but not 5 (64% +8%) years after surgery. In the post-1997 group, more seizure-free patients were taking AEDs at 2 years postsurgery for cases undergoing hemispherectomy (+37%), extratemporal (+22%), temporal (+38%), and multilobar (+50%) resections. In addition, more seizure-free patients with cortical dysplasia (+44%) and atrophic etiologies (+37%) were taking AEDs comparing the post-1997 group with the pre-1997 series.

Complications and reoperations. For the entire series, serious and permanent complications were identified in 39 (9.2%) patients. The complication rate was less in the post-1997 compared with the pre-1997 group (table 3; $p = 0.0016$). There are 11 (2.6%) known deaths. Two deaths occurred during surgery (both in the pre-1997 group) as previously reported.[6] There were 9 long-term deaths involving accidents, status epilepticus, and sudden unexplained death in epi-

Table 3 Seizure outcome of University of California, Los Angeles pediatric epilepsy surgery patients pre- and post-1997[a]

Variable	All years	Pre-1997	Post-1997	p Value
Reporting rate[b]				
6 mo	95% (404/425)	92% (158/172)	97% (246/253)	0.012[c]
1 y	92% (378/412)	87% (149/172)	95% (229/240)	0.0014[c]
2 y	85% (326/382)	83% (143/172)	87% (183/210)	0.271
5 y	75% (236/314)	78% (134/172)	72% (102/142)	0.215
Seizure-free	$p < 0.0001$[c]	$p = 0.0014$[c]	$p = 0.207$	
6 mo	77% (310/404)	67% (106/158)	83% (204/246)	0.0003[c]
1 y	74% (280/378)	63% (94/149)	81% (186/229)	<0.0001[c]
2 y	69% (223/326)	58% (83/143)	77% (140/183)	0.0003[c]
5 y	59% (136/236)	45% (61/134)	74% (75/102)	<0.0001[c]
Seizure category, %[d]	(n = 325)	(n = 143)	(n = 182)	
Always seizure-free	57	40	71	
Never seizure-free	30	42	21	<0.0001[c]
Late seizure recurrence	7	12	5	
Late seizure-free	5	5	9	
Operation location[e]	$p = 0.0006$[c]	$p = 0.071$	$p = 0.0096$[c]	
Hemispheric	75% (106/141)	66% (42/64)	83% (64/77)	0.017[c]
Extratemporal	56% (71/126)	46% (27/58)	65% (44/68)	0.041[c]
Temporal	79% (46/58)	67% (14/21)	86% (32/37)	0.073
Operation type[e]	$p = 0.024$[c]	$p = 0.244$	$p = 0.169$	
Hemispherectomy	75% (106/141)	66% (42/64)	83% (64/77)	0.017[c]
Multilobar	55% (28/51)	50% (17/34)	65% (11/17)	0.320
Lobar/focal	67% (89/133)	53% (24/45)	74% (65/88)	0.017[c]
Histopathology/etiology[e]	$p = 0.0054$[c]	$p = 0.0025$[c]	$p = 0.040$[c]	
Cortical dysplasia	72% (86/120)	68% (36/54)	76% (50/66)	0.343
Atrophy/ischemia	68% (40/59)	57% (17/30)	79% (23/29)	0.063
Tumor	82% (18/22)	71% (5/7)	87% (13/15)	0.388
Hippocampal sclerosis	89% (24/27)	89% (8/9)	89% (16/18)	0.994
Hemimegalencephaly	63% (17/27)	27% (3/11)	87% (14/16)	<0.0001[c]
Rasmussen syndrome	61% (16/26)	61% (8/13)	61% (8/13)	0.997
Tuberous sclerosis	50% (12/24)	0% (0/4)	60% (12/20)	0.028[c]
Nonspecific gliosis	33% (5/15)	33% (4/12)	33% (1/3)	0.998
Sturge-Weber	80% (4/5)	100% (3/3)	50% (1/2)	0.171
Other, %	(n = 425)	(n = 172)	(n = 253)	
Complications	9	14	6	0.0016[c]
Reoperations[f]	10	14	6	0.0025[c]
CSF shunts	19	22	17	0.201

[a] p values over vertical columns indicate statistical test for the column. Horizontal p values indicate statistical tests comparing the pre- and post-1997 groups.
[b] Reported over expected number of patients.
[c] Significant difference ($p < 0.05$). Statistical tests include t tests and χ^2 where appropriate.
[d] For patients with 2 and 5 years of follow-up.
[e] Percent seizure-free at 2 years of follow-up.
[f] Based on year of initial operation.

lepsy (8 in the pre- and 1 in the post-1997 group). The mean (±SD) time from operation until late death was 6.2 ± 4.4 years (range 2–14 years). Five of the late deaths occurred more than 5 years after surgery. There were 6 operative-related intracranial bleeds that required a return to surgery for evacuation (all in the pre-1997 group), 12 infections requiring long-term IV antibiotics (8 in the pre- and 4 in the post-1997 groups), and 4 cases of unanticipated neurologic deficits (cranial nerve palsies, increased motor and language deficits; all in the post-1997 group). In addition, one patient had a posterior cerebral artery infarct on the same side as the hemispherectomy (without increased neurologic compromise), 2 patients had tumor recurrence after an initial epilepsy operation, and 1 patient with TSC developed a subependymal giant cell astrocytoma (SEGA) after epilepsy surgery (all in the post-1997 group).

Reoperations for epilepsy surgery occurred in 42 (9.8%) patients. The mean (±SD) time from first to last operation was 3.1 ± 3.9 years (range 6 days–14 years). Most of the reoperations (29/42; 69%) occurred less than 3 years after the first operation. Most had reoperations to convert a previous multilobar resection into cerebral hemispherectomy (n = 17; 13 in the pre- and 4 in the post-1997 groups). Others had completion of hemispheric disconnection after an unsuccessful first operation (n = 10; 6 in the pre- and 4 in the post-1997 groups), further resection involving lobar/focal operations (n = 9; 5 in the pre- and 4 in the post-1997 groups), multistage reoperations for patients with TSC (n = 3; all post-1997 group), and recurrent tumor (n = 2) or SEGA (n = 1; all post-1997 group). The percentage of patients with reoperations was greater in the pre-1997 group compared with the post-1997 series ($p = 0.0025$).

CSF shunts were necessary in 79 (18.6%) patients in this series. Most CSF shunts were in patients undergoing cerebral hemispherectomy (39.5%; n = 70/177) with fewer patients needing shunts with multilobar (5%; 3/64) and lobar/focal (7%; 6/84) resections. The use of CSF shunts was similar in the pre- and post-1997 groups ($p = 0.201$). For hemispherectomy patients, the need for CSF shunts was greater in the pre-1997 group (47%; 32/68) compared with the post-1997 series (34%; 37/109; $p = 0.05$).

Multivariate analysis. Logistic regression analysis was performed using pre- and post-1997 groups, operation location, operation type, etiology, and use of AEDs at 2 years postsurgery as independent variables in a model with seizure-free cases at 2 years postsurgery as the dependent variable. The period of evaluation (pre- vs post-1997, $p = 0.0001$) and AED use at 2 years ($p < 0.0001$) were associated with greater percentage of patients with seizure-free outcomes, but not operation type, location, or etiology ($p >$

Table 4 Antiepileptic drug use, University of California, Los Angeles pediatric cohort: pre- and post-1997[a]

Variable	All years	Pre-1997	Post-1997	p Value
No. of AEDs, mean ± SD				
Evaluation	2.4 ± 1.0	2.3 ± 1.0	2.5 ± 1.0	0.022[b]
6 mo	1.6 ± 0.8	1.4 ± 0.7	1.7 ± 0.8	0.0002[b]
1 y	1.3 ± 0.9	1.2 ± 0.8	1.4 ± 0.9	0.047[b]
2 y	1.2 ± 1.0	1.0 ± 1.0	1.2 ± 0.9	0.093
5 y	1.2 ± 1.0	1.2 ± 1.0	1.2 ± 1.1	0.954
Patients using AEDs				
6 mo	96% (387/403)	94% (148/158)	97% (239/245)	0.052
1 y	88% (331/378)	84% (125/149)	90% (206/229)	0.079
2 y	78% (255/326)	69% (99/143)	85% (156/183)	0.0005[b]
5 y	77% (182/236)	80% (107/134)	74% (75/102)	0.251
Seizure-free off AEDs[c]				
6 mo	5% (16/308)	9% (10/106)	3% (6/202)	0.015[b]
1 y	15% (43/279)	21% (20/94)	12% (23/185)	0.050[b]
2 y	32% (71/223)	53% (44/83)	24% (27/113)	<0.0001[b]
5 y	40% (54/136)	44% (27/61)	36% (27/75)	0.327
Seizure-free off AEDs				
By operation location[d]	p = 0.260	p = 0.458	p = 0.532	
Hemispheric	37% (39/106)	59% (25/42)	22% (14/64)	<0.0001[b]
Extratemporal	26% (71/126)	44% (27/58)	20% (9/44)	0.031[b]
Temporal	24% (11/46))	50% (7/14)	12% (4/32)	0.0061[b]
Seizure-free off AEDs				
By operation type[d]	p = 0.095	p = 0.196	p = 0.595	
Hemispherectomy	37% (39/106)	59% (25/42)	22% (14/64)	<0.0001[b]
Multilobar	39% (11/28)	59% (10/17)	9% (1/11)	0.0085[b]
Lobar/focal	24% (21/89)	37% (9/24)	18% (12/65)	0.061
Seizure-free off AEDs				
By histopathology/ etiology[d]	p = 0.464	p = 0.265	p = 0.719	
Cortical dysplasia	38% (33/86)	64% (23/36)	20% (10/50)	<0.0001[b]
Atrophy/ischemia	37% (15/40)	59% (10/17)	22% (5/23)	0.017[b]
Tumor	17% (3/18)	33% (1/3)	15% (2/13)	0.814
Hippocampal sclerosis	30% (7/24)	50% (4/8)	19% (3/16)	0.111
Hemimegalencephaly	17% (3/17)	33% (1/3)	7% (1/15)	0.180
Rasmussen syndrome	31% (5/16)	60% (3/5)	45% (5/11)	0.590
Tuberous sclerosis	17% (2/12)	0% (0/0)	17% (2/12)	0.890
Nonspecific gliosis	40% (5/5)	25% (1/4)	100% (1/1)	0.170
Sturge-Weber	25% (1/4)	100% (1/1)	67% (2/3)	0.505

Abbreviation: AED = antiepileptic drug.
[a] Horizontal p values indicate statistical tests comparing the pre- and post-1997 groups.
[b] Significant difference ($p < 0.05$). Statistical tests include t tests and χ^2 where appropriate.
[c] Percent of seizure-free patients not taking AEDs.
[d] At 2 years of follow-up.

0.081). In other words, better postsurgical seizure-free outcomes were linked with having surgery after 1997 and with less aggressive withdrawal of AEDs after surgery.

DISCUSSION Despite similarities in age at seizure onset, age at surgery, epilepsy duration, and other presurgical clinical variables, this study identified differences in presurgical and postsurgical clinical variables comparing the first 11 years (pre-1997) with the second 11 years (post-1997) of our program. Compared with the pre-1997 group, the post-1997 series showed more resection and palliative operations per year, more lobar/focal and fewer extratemporal and multilobar resections, more patients with TSC and fewer cases with nonspecific gliosis, fewer patients with diagnostic intracranial electrode studies, a higher rate of patients seizure-free at all measured time points after surgery, a lower proportion of seizure-free patients not taking AEDs at 0.5, 1, 2, and 5 years postsurgery, and fewer operative complications and reoperations. Logistical regression identified the period of surgery (pre- vs post-1997) and AED use after surgery as the most important predictors of becoming seizure-free. Taken together, these results indicate that over time there were sustained improvements in pediatric epilepsy surgery patients at the UCLA program.

The improvement in surgical outcome for pediatric epilepsy surgery patients was likely due to multiple overlapping and interacting factors, not a single reason. These factors would include better presurgical noninvasive technology to identify epileptogenic lesions, improved selection of potential surgical candidates, and our conscious decision to completely remove the lesion at surgery and alter postoperative AED management after 1997. For example, the use of stronger MRI magnets with better software, thinner slice FDG-PET scans, and incorporation of FDG-PET/MRI coregistration, MSI, and fMRI into the presurgical evaluation process likely improved the identification of the epileptogenic zone and important functional cortex.[15-19] Better neuroimaging technologies and experience in using them probably explain the decrease in patients with nonspecific gliosis in the post-1997 series. Improved neuroimaging probably also explains the increase in the percent of patients with focal/lobar operations compared with multilobar resections after 1997.[17,20] Likewise, changes in practice, such as not reducing AEDs so quickly after surgery in seizure-free patients, were associated with better outcomes. Improved surgical procedures, such as for cerebral hemispherectomy, were likely related to better outcomes, reduced complications, and reoperations in the post-1997 group.[21-23]

We also learned over time the importance of performing complete resections in pediatric epilepsy surgery patients.[24,25] Before 1997, we often restricted our cortical excisions to prevent neurologic deficits

such as performing multilobar temporal-occipital-parietal resections in patients with mostly posterior MRI findings and an incomplete hemiparesis. However, we found in the pre-1997 group that a significant number of patients with incomplete operations were not seizure-free with longer follow-ups and needed additional surgery often 2 or more years after the initial operation. Since 1997, we have altered our approach and advocated for complete resections with the initial operation, especially in young children at risk for epileptic encephalopathy, even if that means removing the motor-sensory cortex and other partially functional cortex.[26] More complete resections might explain the better and persistent seizure control at 2 and 5 years of follow-up in the post-1997 series.[17,26] The number of reoperations, and eventual seizure-free patients off medications with longer follow-up durations, are similar between our series and the literature.[10,27-30]

Phase II intracranial EEG studies were used at a lower rate than usually reported. The ILAE survey of 20 pediatric epilepsy surgery centers involving 543 children found that intracranial electrodes were used in 27% of patients.[3] Furthermore, 9% to 73% of pediatric patients were reported to use intracranial electrodes in previous surgical cohorts.[5,8,9,11-13] Our lower rate of intracranial electrode implantation is probably attributable to our approach of using multiple noninvasive technologies and intraoperative ECoG to identify the zone of cortical abnormality likely responsible for epileptogenesis. This is a different approach than targeting areas of EEG ictal onsets for resection.[31,32]

Our study from a single center achieved high reporting rates for seizure outcome. However, the reader should note that our series has a higher proportion of younger patients, more cases of hemispherectomy, and fewer cases of temporal lobe resections compared with other cohorts from pediatric epilepsy surgery centers.[3,7,8,11-13,28] Thus, comparisons of outcomes may or may not be similar when other centers report their long-term findings.

The reader should be aware of the inherent limitations of our study. For example, this was a retrospective analysis. As such, we can only infer cause and effect from our findings. Prospective multicenter studies will be necessary to determine if the presurgical evaluation, surgical approach, completeness of resection, and AED use after surgery is linked with the best postsurgical seizure-free outcomes.[33] Likewise, we did not assess cognitive and developmental outcomes.[22,34,35] Over the 22 years we have found it more difficult to obtain approval of these studies from insurance companies. Thus, it is possible that some patients were cognitively improved despite not being seizure-free after surgery. Finally, we have 5-year outcome data on a proportion of patients in the post-1997 series. As we have learned from our analysis, we will need to follow this cohort to determine if the findings related to seizure control, late deaths, and reoperations remain valid.

This study is pertinent for the practicing neurologist because it indicates that with improved technologies and greater clinical experience including management of postoperative medications a significant proportion of pediatric patients can expect to become seizure-free after surgery. This finding emphasizes the conclusion of the ILAE Sub-Commission on Pediatric Epilepsy Surgery that all children with therapy-resistant epilepsy of unknown etiology should be referred to an experienced center for diagnostic evaluation and surgical consideration.[4] These children are at risk for epileptic encephalopathy, and some may be candidates for cortical resections with a high chance of becoming seizure-free if an experienced surgical team can identify a surgically treatable etiology and remove it.[22,34,35] Even if not a resection candidate, these children may be offered alternate treatments, including palliative operations.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Gary W. Mathern.

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ANEXO C - ARTIGO EM INGLÊS

Hippocampal damage in type I focal cortical dysplasia is linked to an initial precipitating injury

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Statistical analysis was conducted by the corresponding author.
Counts: Title: 84 characters, Abstract: 1 double spaced page, Text: 12 pages. Figures: 2; Tables: 3. References: 32.
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ABSTRACT

Background: Focal cortical dysplasias (FCD) are the most common etiological substrate in pediatric epilepsy surgery. Type I FCD patients frequently have hippocampal sclerosis (HS), but the mechanisms underlying hippocampal damage in such patients is unknown. In this study, we performed a clinical-pathological study to identify the pathogenic mechanisms of hippocampal damage in children with refractory temporal lobe epilepsy (TLE) associated with FCD.

Methods: We included patients with refractory epilepsy operated on the temporal lobe, whose neuropathological examination revealed FCD (FCD type I and II groups). As comparison groups, we included patients with temporal low-grade tumors (LGT group), patients with TLE without neocortical lesions, with or without hippocampal sclerosis (HS/NNL group), and autopsy controls (Autopsy group). Clinical variables were correlated with the presence of hippocampal damage evaluated by MRI, histopathology and neuronal densities.

Results: A total of 108 children were included in the study, 41 patients in the HS/NNL group (38%), 32 in FCD type I group (29.6%), 20 patients in LGT (18.5%), 5 patients in FCD type II group (4.6%), and 10 autopsy cases (9.3%). The prevalence of na initial precipitating injury (IPI) was low in LGT group, intermediate in FCD type I and II groups, and high in HS/NNL group (P<0.001). Half patients in the FCD type I group had hippocampal damage in qualitative studies, and lower neuron densities in several hippocampal subfields when compared with Autopsy group. The analysis showed that, in FCD type I and HS/NNL groups, the presence of an IPI was associated with lower neuronal densities in fascia dentate and Sommer's sector (CA1 and prosubiculum).

Conclusion: Our results support the view that, similar to mesial temporal lobe epilepsy associated HS (MTLE-HS) patients, the mechanism of hippocampal damage frequently seen in type I FCD patients appears to be related to an IPI.

INTRODUCTION

Focal cortical dysplasias (FCD) are the most common etiological substrate in pediatric epilepsy surgery[1] and one of the most common substrates in adults.[2-4] According to the most recent classification scheme, FCDs are distinguished between mild type I and severe type II.[5] Type I FCDs may be characterized exclusively by cortical disorganization and dyslamination (type IA FCDs), or may also include hypertrophic pyramidal neurons outside layer V (type IB FCD). Beside the architectural disturbances of cortical lamination seen in Type I, Type II FCDs present with gross histopathological changes including dysmorphic neurons (FCD type IIA) or balloon cells (FCD type IIB). Though belonging to the same pathological category, patients with type I and type II FCDs have different clinical profiles. Patients with type I FCD frequently have a more widespread disease, more severe cognitive impairment, and poorest postsurgical seizure outcome.[6, 7] Patients with type II FCDs are younger at seizure onset, younger at surgery, and have increased seizure frequency when compared with those with type I.[8]

Different pathogenic mechanisms appear to be implicated in the genesis of different FCD types. Type II FCDs, characterized histologically by the presence of abnormal cell types that failed to differentiate at early stages of development, are probably secondary to abnormal cell proliferation. On the other hand, type I FCDs are considered secondary to abnormal cortical organization, acquired in late stages of cortical development, after most of the period of cell proliferation was completed.[2, 3] Supporting this theory, type I FCD patients more frequently have temporal lobe epilepsy (TLE) and a history of perinatal problems, when compared to patients with type II FCD. In addition, type I FCD is frequently associated with hippocampal sclerosis (HS), a most likely acquired pathology.[7, 9] However, the mechanisms that lead to hippocampal damage in children with FCD are still not completely understood. Evaluating the relationship between FCD and HS is important not only to understand the mechanisms underlying hippocampal damage in FCD patients, but it may also have implications to clinical management. For example, it has been shown that when both substrates are present (dual-pathology), surgical removal of both the FCD and atrophic hippocampus is the best surgical approach.[10, 11] Therefore, during

presurgical evaluation, the identification of clinical characteristics and events that predispose patients with FCD to develop HS or characteristics of patients with HS that suggest the presence of FCD, would suggest the presence of dual pathology, that warrants a more precise definition of the true epileptogenic area prior to surgical treatment.

Clinical-pathological studies in children and adults with TLE performed by our group have identified that the mechanisms of seizure-related hippocampal damage are linked to an initial precipitating injury (IPI), yet additional hippocampal damage can occur due to chronic limbic seizures.[12-14] In this study, we performed a clinical-pathological study to identify the pathogenic mechanisms of hippocampal damage in children with refractory TLE associated with FCD.

PATIENTS AND METHODS

Study design and setting

Study design: This is a case-control study to investigate the mechanisms of hippocampal damage in children with FCD. The study groups (cases) included patients with refractory epilepsy operated on the temporal lobe, whose neuropathological examination revealed FCD (FCD type I and II groups). As comparison groups (controls), we included patients with temporal low-grade tumors (LGT group), patients with TLE without neocortical lesions, with or without hippocampal sclerosis (HS/NNL group), and autopsy controls (Autopsy group). Then, clinical variables were extracted from the charts and correlated with the presence of hippocampal damage evaluated by qualitative (MRI and histopathological) and quantitative (neuronal densities) methods. Finally, we performed multivariate and stratification analysis to control for possible confounding variables.
Setting: Fifty-nine children were from University of California, Los Angeles, USA, operated between 1996 and 2008 (UCLA). Thirty-nine children were from Faculdade de Medicina de Ribeirão Preto, Brazil, operated between 2001 and 2008 (FMRP-USP). All patients had drug resistant epilepsy, defined as failure of two different appropriate anti-epileptic drugs (AEDs) to bring seizures under complete control when used as prescribed and pushed to the maximum tolerated levels.[15] All autopsy controls were from Ribeirão Preto. Informed consent was obtained to use clinical data for research studies in both institutions.

Case ascertainment and control selection

All patients included in this study were submitted to TL surgery because their presurgical evaluation workups had suggested the TLE as the origin of seizures. The TL to be resected was defined based on the convergence of video-EEG monitoring and neuroimaging abnormalities. The clinical protocols have been previously published elsewhere.[16, 17] In brief, the presurgical evaluation workup included detailed history and neurologic examination, interictal and ictal scalp EEG, and, when necessary, intracarotid amobarbital injections (Wada test) or functional MRI for evaluation of memory or speech representation in both institutions. Neuroimaging

studies included 1.5T MRI (UCLA and FMRP-UCLA), ^{18}fluoro-2-deoxyglucose PET (FDG-PET, only UCLA), and ictal SPECT (only FMRP-UCLA). Finally, at surgery, electrocorticography further defined the extension of the brain regions to be removed based on background slowing, location of interictal spikes, and ictal discharges (UCLA and FMRP-UCLA).

FCD group: Patients with refractory TLE whose histopathological examination of resected tissue revealed FCD were included in this group. After reviewing the neuropathology reports, patients were further classified according to Palmini's classification scheme in mild type I and severe type II FCD, as follows.[5] If histopathological examination revealed cortical disorganization and dyslamination or hypertrophic neurons without abnormal dysmorphic neurons or balloon cells, were classified as Type I FCD. Those with cortical disorganization and dyslamination plus abnormal dysmorphic neurons or balloon cells were classified as Type II FCD.

LGT group: Patients with refractory TLE whose histopathological examination revealed low-grade tumors were included in this group. Histopathological diagnosis of LGT was defined according the current WHO classification.[18]

HS/NNL group: In this group, we included all patients with TLE whose neuropathological examination did not reveal any other lesion other than hippocampal sclerosis (HS). MRI-negative patients were also included if history, clinical examination, video-EEG monitoring, and neuroimaging studies clearly suggested TLE.

Autopsy controls: For comparison purposes, hippocampal tissue was obtained from autopsy of children with similar age without neurological disease. Death in the autopsy group was from acute cardiac, sepsis, or traumatic causes. The median (range) post mortem delay was 7.5 hours (5.5 to 14).

Variables

Evaluation of hippocampal damage

Qualitative MRI: MRI scans performed in a 1.5T scanner were reviewed for the qualitative presence/absence of hippocampal abnormalities, namely increased signal changes in T2-weighted sequences and atrophy in T1-weigheted MRI.

Hippocampal tissue processing: At surgery, a standard *en bloc* anterior resection including 3-4 cm of the hippocampus was performed. One or more 1.5-2 cm blocks of

neocortex and adjoining white matter were microsurgically removed and the blocks were immersion-fixed for immunocytochemistry.

Qualitative histopathological assessment of hippocampal damage: The hippocampal slides were reviewed by two examiners (TRV and GWM) and classified as normal (no-HS), classical hippocampal sclerosis (classical-HS), severe hippocampal sclerosis (severe-HS), or undetermined. Hippocampi without hippocampal cell loss were classified as no-HS. Those with severe neuron loss in Sommer's sector [CA1 and Prosubiculum (PRO)] and endfolium (hilus and CA4), associated with some neuron loss in fascia dentata (FD) and CA3, but relative preservation of CA2 and subiculum (SUB) were classified as classical-HS. If the hippocampal neuron loss was more severe and widespread, we classified as severe-HS. Hippocampi missing several subfields and those with preparation artifacts, preventing a proper classification, were classified as undetermined. Hippocampi classified differently by the two examiners were reviewed together to reach a consensus.

Hippocampal neuron densities: Hippocampal sections were stained with cresyl violet for neuron counts (10µm sections). The neuron counts were performed by one person (MH), blind for the clinical and neuroimaging data. Cell count procedures followed previously published protocols.[19] Briefly, counts were performed at 400x using an ocular grid. For stratum pyramidale, 20 boxes in sequential 2 x 2 box segments (104 x 1040 µm) were selected; for the smaller granule cells, a linear 1 x 5 box was used (52 x 260 µm), and counts over four such areas (both top and bottom granule cell blades) were averaged. Neuronal densities were computed as: $N(\text{neurons/mm}^3) = A[M/(L + M)]$ divided by the volume of the sampling area (10 µm x area of grid), where A is the number of counted nuclei, L is the average length of the nucleus, and M is the section thickness.[19] The subfields evaluated were the granule cells of upper and lower fascia dentate (FDU and FDL), CA4, CA3, CA2, CA1 stratum pyramidal, PRO, and SUB neurons. The results are given in number of cells per cubic millimeter (cells/mm^3), reflecting estimates of the number of neurons per unit volume, not "absolute" calculations of total neurons per hippocampus. Because stereological methods for estimating total neurons require availability of the entire hippocampus, they are not feasible for surgical specimens. In addition, we are aware that, due to the injury-induced shrinkage of their somata, Nissl-stained neurons can be more difficult to differentiate from the surrounding glia in comparison with neuronal-specific staining methods. However, as the tissue from all groups were

processed and counted similarly, statistical differences in neuron densities can be accepted as valid.[19-21] Finally, as we did not measure stratum granulosum width, lower densities in FD may reflect only granule cell dispersion, more than real neuron loss.

Clinical variables

To evaluate the clinical variables associated with hippocampal damage, the charts from all patients were reviewed and clinical variables abstracted from the files. The data included age at seizure onset, age at surgery, epilepsy duration, gender, seizure frequency per month, seizure type (complex partial or generalized seizures), and presence of an IPI. An IPI was defined as any medical event or incident of probable cerebral injury associated with unconsciousness for at least 30 min or alteration in cognition for more than 4 hours.[22] This information was collected retrospectively from the various presurgical evaluation interviews, without knowledge of the hippocampal pathology. The IPIs were classified as seizure (febrile seizures, *status epilepticus*) or non-seizure types (meningitis, encephalitis, or head trauma).[22]

Statistical analysis

To evaluate differences between categorical variables among groups we used Chi-square test. To obtain an accurate significance level in tables with 0 cell counts or tables with more than 20% of cells with counts lower than 5, we used Exact Tests. For numerical variables, variables were evaluated using Student t (2 groups) or ANOVA tests (more than 2 groups) for normally distributed variables, or their correspondent (Mann-Whitney and Kruskal-Walis tests) for non-normally distributed numerical variables. Post-hoc analysis after ANOVA tests were performed using Games-Howell test for unequal variances. Correlation between two numerical variables was evaluated using the Spearman correlation test.

To control for confounding we used simple stratification methods or multivariable analysis [General Linear Model univariate (ANCOVA)]. For some hippocampi, one or more subfields were injured during the surgical procedure, resulting in missing data for these subfields. However, missing data analysis revealed that these events occurred completely at random (P=0.399, Little's MCAR test). The SPSS® package (release 16.01) was used for statistical analysis.

RESULTS

Clinical characteristics of study participants

A total of 108 children were included in the study, 41 patients in the HS/NNL group (38%), 32 in FCD1 group (29.6%), 20 patients in LGT (18.5%), 5 patients in FCD2 group (4.6%), and 10 autopsy cases (9.3%). The prevalence of patients with type II FCDs occurring exclusively in the TLE in our series was low. The histopathological diagnosis of LGTs were dysembryoplastic neuroepithelial tumor (N=9), ganglioglioma/gangliocytoma (N=7), and oligodendroglioma (N=4). Fifty-two individuals were female (48.1%). The median (range) age at seizure onset was 4 years (0.1 to 15), the median age at surgery was 12 years (1 to 18), the median epilepsy duration was 6.5 years (0.5 to 16), and the median seizure frequency was 18 seizures per month (1 to 500). There were no differences between the age of death in the autopsy group and age of surgery in patients with TLE (mean difference = 1.8 year, *P*=0.429, Mann-Whitney U test). The etiological profile of UCLA patients was different from FMRP-USP patients, with type I FCD patients more frequent at UCLA and HS/NNL patients more frequent at FMRP-USP (*P*=0.008, Exact test). However, other variables such as age at seizure onset, age at surgery, epilepsy duration, and the percentage of patients seizure-free after surgery were similar between the two locations (data not shown).

Table 1 shows the clinical characteristics of the participants divided by neuropathological category. The groups were similar in relation to age of seizure onset (*P*=0.820; ANOVA), but the age at surgery was higher in HS/NNL group when compared with LGT and FCD type II groups (*P*=0.014; ANOVA). This resulted in a lower epilepsy duration in these groups when compared with HS/NNL (*P*=0.013; ANOVA). In addition, seizure frequency in both FCD groups was significantly higher than HS/NNL and LGT groups (*P*=0.002; ANOVA). There were no differences in relation to gender and the proportion of patients with complex partial seizures between groups (*P*=0.848 and *P*=0.360; respectively). The prevalence of IPI was significantly different between groups (*P*<0.001, Exact test), with a low prevalence in LGT group (0%), intermediate in FCD type I and II groups (40% and 47%; respectively), and high in HS/NNL group (80%). The IPI type was similar between groups. A seizure-type IPI was more frequent in all subgroups, being found in both patients with IPI in FCD type II group, 67% of patients with IPI in FCD type I group,

and 70% of HS/NNL group (*P*=1.0, Exact test).
Ninety patients had at least one year of postsurgical seizure outcome available for analysis. The mean (±SD) follow-up time was 3.6 (2.7) years and the overall percentage of seizure-free patients was 79%. The proportion of seizure-free patients was similar between groups (*P*=0.360, Exact test), with 93% of seizure freedom in LGT, 81% in FCD type I, 80% in FCD type II, and 72% in HS/NNL group.

Prevalence of hippocampal damage according to neuropathological category
MRI qualitative assessment: As expected, the analysis of MRI scans showed that the proportion of patients with hippocampal abnormalities was high in HS/NNL group (93%). Dual pathology of the TL (hippocampal atrophy and increased signal intensity associated with FCD) was observed in a sizable proportion of FDC type I (50%) and FCD type II groups (40%). In patients with LGT MRI signs of hippocampal was observed in a small proportion (27%, *P*<0.001, Exact Test). For details, see Table 1.
Qualitative histopathological assessment of hippocampal damage: Eighty-five hippocampal specimens were available for qualitative assessment (79% of cases). Similar to MRI analysis, the proportion of patients with hippocampal sclerosis was significantly different between groups (*P*<0.001, Exact test), with a higher proportion in HS/NNL group (80%), intermediate in FCD type I group (41%), low in LGT group (20%), and 0% in Autopsy group. Only 3 patients in the FCD type II group had hippocampal specimens available for analysis, 2 patients were classified as no-HS and 1 patient as undetermined. Finally, the proportion of patients with severe HS was higher in HS/NNL group, when compared with other groups (*P*<0.001, Exact test). For details, see Table 1.
Hippocampal neuron densities: Figure 1 shows the neuronal densities displayed by neuropathological category. Post-hoc analysis showed that the neuronal density was lower in HS/NNL group when compared with Autopsy in all subfields (*P*<0.001 to *P*=0.013), except SUB (*P*=0.077). In FDU and CA1, the neuronal density in HS/NNL was lower than all other groups. The neuronal densities in CA4 and CA3 were significantly lower in FCD type I group when compared with Autopsy (*P*=0.002 and *P*<0.001, respectively). In SUB, type I FCD neuronal densities were lower than other groups, but not significantly (*P*=0.077). The neuronal densities in LGT and FCD type II groups were similar to Autopsy group in all subfields.
In summary, the evaluation of hippocampal damage by qualitative (MRI and

histopathology) and quantitative estimation of hippocampal neuron densities revealed similar results. As expected, HS was more prevalent in HS/NNL group. However, about 40-50% of patients in FCD type I group had hippocampal involvement in qualitative studies, and several hippocampal subfields had lower neuron densities when compared with Autopsy. The percentage of patients from LGT group with hippocampal involvement was low in qualitative analysis (20-27%) and the neuronal densities were similar to Autopsy group in quantitative histopathological analysis.

Correlation between clinical variables and hippocampal damage

Univariate analysis

Table 2 shows the univariate analysis of neuronal densities for each hippocampal subfield in relation to clinical variables (neuropathological category, presence/absence of an IPI, epilepsy duration; age at surgery, age of seizure onset, and seizure frequency). As expected, the neuronal densities were associated with the neuropathological category in all subfields. The neuronal densities also correlated with epilepsy duration in FDL, CA2, and CA1; with age at surgery in FDL, CA4, CA2, and CA1; and with age of seizure onset in CA4. There were no correlation between seizure frequency and the neuronal densities in any subfield of hippocampal formation. In most subfields, there was a correlation between the neuronal densities and the presence of an IPI (FDU, FDL, CA4, CA3, CA1, and PRO). Of note, all patients with severe HS in HS/NNL and FCD1 groups had a positive history of IPI.

Multivariate analysis

Because neuropathological category was associated with neuronal densities and the presence of an IPI and age at surgery, we performed a multivariate analysis to control for confounding (General Linear Model-ANCOVA). The independent variables included in the model were neuropathological category and presence/absence of IPI as factors; and epilepsy duration and age at surgery as covariables (Table 3). Because the small sample size in FCD type II group and the absence of patients with an IPI in LGT group, both groups were excluded from the multivariate analysis. The analysis showed that, in FCD type I and HS/NNL groups, the presence of an IPI was independently associated with lower neuronal densities in FD and Sommer's sector (CA1 and PRO), even controlling for the neuropathological category, age at surgery,

and epilepsy duration. When controlled for age at surgery, epilepsy duration was not correlated with neuronal densities in any hippocampal subfield (see Table 3 for details). Therefore, multivariate analysis showed that the presence of an IPI was the most important variable associated with hippocampal damage in both type I FCD and HS patients.

To illustrate the association between IPI and neuron densities we stratified patients with type I FCD and HS/NNL in those without or with IPI (Figure 2). The stratification analysis showed that neuron densities in patients with FCD type I without IPI were similar to Autopsy in all subfields, except CA3. On the other hand, neuron densities in FCD type I patients with IPI were very similar to HS/NNL with IPI. In fact, post-hoc analysis (Games-Howell test) revealed that in FDU, FDL, CA4 and PRO the neuron densities were lower in type I FCD patients with a history of an IPI when compared with Autopsy. In CA1, HS/NNL patients with a history of IPI had lower densities when compared with FCD type I patients with IPI (Figure 2).

DISCUSSION

Previous studies have shown that hippocampal damage is frequently found in patients with type I FCD. In mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS), we have shown that hippocampal neuron loss is probably related to events occurring in infancy and childhood (IPI),[13, 14, 23-27] but the mechanisms causing hippocampal damage in children with type I FCD are still not completely understood. To address this question, we performed a clinical-pathological study in a series of children with TLE. Our results showed that 50% of children with type I FCD had significant hippocampal damage and 47% had a history of an IPI. We also found that lower hippocampal neuron densities were strongly associated with a history of IPI, even controlling for confounding variables. Hippocampal neuron loss was not associated with other clinical variables, such as seizure frequency, age at surgery, and epilepsy duration. Taken together, our results support the notion that, similar to MTLE-HS patients, the hippocampal damage in patients with type I FCD is most likely an acquired pathology resulting from an IPI.

Interpretation of study's results

Our results are in line with other studies showing that type I FCD occur frequently in the TL in association of hippocampal damage (dual pathology), while type II FCD is rarely found exclusively in the TL.[6, 7, 9, 28] The frequent localization of type I FCD lesions within the TL is one of the postulated theories for the development of hippocampal damage in such patients. Because of its proximity to the hippocampus, chronic and frequent limbic seizures could result in neuronal loss, while seizures arising from extratemporal lesions would not.[29] This could explain, for example, why dual pathology is less frequent in type II FCD patients, since it is rarely found exclusively in the TL. However, contradicting this theory, patients with LGT localized in the TL rarely had MRI or histopathological evidence of hippocampal damage (27%) in our series, as previously reported by other studies.[30] In addition, previous studies have shown that malformations of cortical development are associated with hippocampal atrophy independent of the distance of the lesion from the hippocampal formation.[30] Finally, hippocampal neuron densities in our series did not correlate with seizure frequency or epilepsy duration, suggesting other mechanisms for the neuronal loss other than an exclusive kindling-like mechanism.

Our study is in agreement with other studies showing the common occurrence of perinatal and postnatal events in patients with mild type I FCD.[6] Using quantitative methods to evaluate hippocampal neuronal loss, we found that in TLE patients with type I FCD a history of IPI was associated with decreased hippocampal neuronal densities in FD and Sommer's sector (CA1 and PRO). On the other hand, LGT patients had no history of an IPI and hippocampal damage revealed by MRI and histopathology was uncommon (27% and 20%, respectively). Moreover, while type I FCD patients without a history of IPI had hippocampal neuron densities similar to autopsy cases without neurological disease, type I FCD patients with a history of IPI had a neuron loss pattern very similar to classical HS patients with a history of IPI (Figure 2). Taken together, our data suggest that the mechanism of hippocampal neuron loss in patients with type I FCD was related to the IPI, which was confirmed by multivariate analysis that controlled for confounding. In other words, our data support the idea that a pre-existing lesion (type I FCD) may predispose late events in childhood (prolonged seizures or *status epilepticus)*, which may result in hippocampal damage.[31]

We cannot exclude, however, that the same pathogenic mechanism responsible for the development of type I FCD might have contributed for the development of hippocampal damage. As stressed before, mild type I FCDs are believed to be secondary to late events during brain development, which might alter local cell maturation and result in abnormal cortical organization and giant, dysplastic cells.[4] This idea is supported by previous descriptions of cytoarchitectural disorganization, abnormal arrangement of neurons, and hypertrophic neurons in primarily undamaged cortex of children with perinatal brain damage (acquired cortical dysplasia).[32] Therefore, it is possible that events occurring in late periods of brain development could result in both acquired FCDs and hippocampal damage. This could predispose children to a second insult occurring late in life (IPI), resulting in additional hippocampal damage. Then, after a latent period when changes in the brain that involve neuroplasticy in response to both events occur, resulting in excess excitability and late TLE. Supporting this idea is the fact that, in our series, classic HS was found in patients without a history of an IPI, but all patients with severe HS revealed by qualitative histopathological analysis had a history of an IPI.

In relation to patients in the HS/NNL group, our study showed that the prevalence of an IPI was as high as in adult series.[12] It also confirmed our previous findings that

children with TLE had neuron losses in an amount and pattern similar to adults with TLE, with greatest cell loss in Sommer's sector (CA1 and PRO) and CA4, and relative sparing of CA2.[13] As the mean age at surgery of HS/NNL patients in our series was only 13 years, our study supports the notion that, although some additional damage can be a result of chronic limbic seizures, most hippocampal damage is already present in early stages of the disease, as suggested previously.[14]

Study limitations

Limitations of the study are the fact that this is a pediatric cohort, with a different clinical profile compared with adult series (lower age of seizure onset and age at surgery, higher seizure frequency, and smaller latent periods). In addition, although we combined the series of two institutions to increase sample size, we still had a small size for subgroup analysis. Finally, as we performed a clinical pathological study evaluating hippocampal tissue, we included only TLE patients, which limited our ability to make inferences about FCDs localized in other brain regions. Further studies using volumetric neuroimaging techniques can confirm the concept proposed in this study and evaluate the role of the localization of FCDs in the development of hippocampal damage.

On the other hand, we should note that, by including only pediatric epilepsy patients, we had the opportunity to evaluate and test pathogenic hypothesis in very early stages of the disease, which enabled us to confirm concepts generated by studies performed mostly in adults. Finally, as we included patients from two sites, we believe that we increased the external validity and, consequently, the generalizability of our findings.

In conclusion, our results support the view that, similar to MTLE-HS patients, the mechanism of hippocampal damage frequently seen in type I FCD patients is related to an IPI. From the perspective of presurgical evaluation, our study showed that patients with type I FCD have a much higher seizure frequency than patients with MTLE-HS. Therefore, in patients with hippocampal atrophy on MRI, an unusually high seizure frequency should suggest the presence of dual pathology. In patients with MRI evidence of FCD, dual pathology is more likely if a history of an IPI is identified. In both situations, a careful assessment of the extent of the epileptogenic zone is warranted.

Table 1. Clinical characteristics of participants divided by neuropathological category.

		Autopsy N=10	LGT N=20	FCD2 N=5	FCD1 N=32	HS/NNL N=41	*P*-value
Age of seizure onset (mean ± SD)		NA	4.8 ± 3.7	3.3 ± 3.5	4.5 ± 3.7	4.9 ± 3.4	*P*=0.820[a]
Age at surgery (mean ± SD)		9.7 ± 6.3	9.9 ± 4.5*	8.2 ± 3.5*	11.2 ± 4.9	13.2 ± 3.5*	***P=0.014***[a]
Epilepsy duration (mean ± SD)		NA	5.0 ± 3.6*	4.9 ± 2.3	6.7 ± 4.2	8.3 ± 3.9*	***P=0.013***[a]
Seizure frequency (mean ± SD)		NA	51.8 ± 77	170 ± 220*	201 ± 221*	61.4 ± 132	***P=0.002***[a]
Gender (female) – n (%)		5 (50%)	11 (55%)	3 (60%)	13 (41%)	20 (49%)	*P*=0.848[b]
IPI (Yes) – n (%)		NA	0 (0%)	2 (40%)	15 (47%)	33 (80%)	***P<0.001***[b]
Complex partial seizures – n (%)		NA	17 (94.4%)	5 (100%)	31 (97%)	41 (100%)	*P*=0.550[b]
Hippocampal abnormality MRI – n (%)		NA	4 (27%)	2 (40%)	16 (50%)	38 (93%)	***P<0.001***[b]
Qualitative evaluation of hippocampal damage	No-HS	10/10 (100%)	15/18 (80%)	2/3 (67%)	11/29 (38%)	2/36 (6%)	***P<0.001***[b]
	Classical HS	0	2/18 (13%)	0	11/29 (38%)	22/36 (61%)	
	Severe HS	0	1/18 (7%)	0	1/29 (3%)	7/36 (19%)	
	Undetermined	0	0	1/3 (33%)	6/29 (21%)	5/36(14%)	
Seizure-free after surgery – n (%)		NA	14/15 (93%)	4/5 (80%)	25/31 (81%)	28/39 (72%)	*P*=0.360[b]

Table 2. Univariate analysis of the association between neuronal densities and clinical variables.

Subfields	Neuropathological category[a]	IPI (yes/no)[b]	Epilepsy duration[c]	Age at surgery[c]	Age of seizure onset[c]	Seizure frequency[c]
FDU	***P*=0.011**	***P*=0.003**	*P*=0.469	*P*=0.700	*P*=0.994	*P*=0.109
FDL	***P*=0.012**	***P*<0.001**	***P*=0.034**	***P=0.024***	*P*=0.769	*P*=0.728
CA4	***P*=0.002**	***P*=0.028**	*P*=0.066	***P*=0.004**	***P*=0.031**	*P*=0.799
CA3	***P*<0.001**	***P*=0.031**	*P*=0.295	*P*=0.078	*P*=0.062	*P*=0.800
CA2	***P*=0.018**	*P*=0.214	***P*=0.001**	***P=0.008***	*P*=0.508	*P*=0.941
CA1	***P*<0.001**	***P*<0.001**	***P*=0.007**	***P=0.018***	*P*=0.790	*P*=0.614
PRO	***P*=0.011**	***P*=0.006**	*P*=0.136	*P*=0.113	*P*=0.765	*P*=0.393
SUB	***P*=0.018**	*P*=0.448	*P*=0.544	*P*=0.074	*P*=0.435	*P*=0. 745

IPI is initial precipitating injury, FDU upper fascia dentate, FDL lower fascia dentate, CA1 to CA4 the subfields of cornu Ammonis, PRO prosubiculum, and SUB subiculum.

a = One-way ANOVA; b = Student t-test; c = Spearmann correlation test.

Table 3. General Linear Model multivariate analysis (ANCOVA) for FCD type I and HS/NNL groups.

Subfields	Neuropathological category	Presence of IPI	Epilepsy duration	Age at surgery	Interaction[a]	Corrected Model
FDU	***P*=0.011**	***P*=0.042**	*P*=0.401	*P*=0.173	*P*=0.099	***P*=0.004**
FDL	*P*=0.059	***P*=0.003**	*P*=0.419	*P*=0.804	*P*=0.226	***P*<0.011**
CA4	*P*=0.669	*P*=0.172	*P*=0.481	***P*=0.014**	*P*=0.669	***P*=0.019**
CA3	*P*=0.958	*P*=0.142	*P*=0.825	*P*=0.187	*P*=0.998	*P*=0.278
CA2	*P*=0.973	*P*=0.765	*P*=0.249	*P*=0.110	*P*=0.126	***P*=0.015**
CA1	***P*=0.037**	***P*=0.025**	*P*=0.413	*P*=0.461	*P*=0.899	***P*<0.001**
PRO	*P*=0.952	***P*=0.012**	*P*=0.143	*P*=0.413	*P*=0.461	***P*=0.012**
SUB	*P*=0.144	*P*=0.389	*P*=0.948	*P*=0.814	*P*=0.884	*P*=0.532

IPI is initial precipitating injury, FDU upper fascia dentate, FDL lower fascia dentate, CA1 to CA4 the subfields of cornu Ammonis, PRO prosubiculum, and SUB subiculum.
a = Interaction between the 2 factors (neuropathological category and presence of IPI);

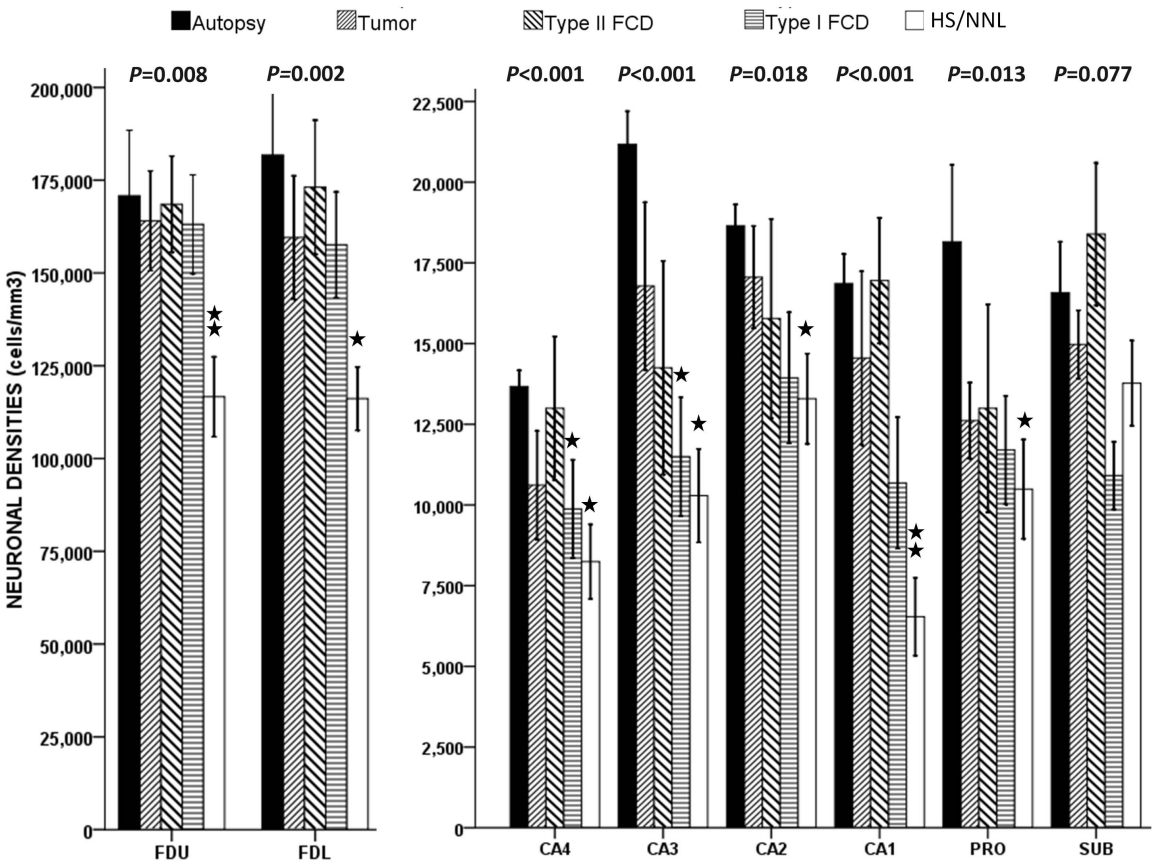

Figure 1 - The bar graphs show the neuronal densities (mean ± SEM) in specific subfields of hippocampal formation between the neuropathological categories. The ANOVA P-values are shown above each subfield and significant post-hoc differences are shown in asterisks (ANOVA Games-Howell test). The neuronal densities were different between groups in all subfields (P<0.001 to 0.013; ANOVA), except SUB (P=0.077; ANOVA). Post-hoc analysis revealed that in FDU and CA1, the neuronal densities were lower in HS/NNL than all other categories (P=0.008 and P<0.001, respectively). In FDL, CA2 and PRO, the neuronal densities in HS/NNL were lower than Autopsy group, but similar to other etiologies (P=0.018, P=0.002, and P=0.013, respectively). In CA4 and CA3 densities were lower in HS/NNL and Type I FCD in comparison with Autopsy (P<0.001). In SUB, type I FCD neuronal densities had a tendency to be lower than Autopsy and FCD type II cases, but not significantly (P=0.077).

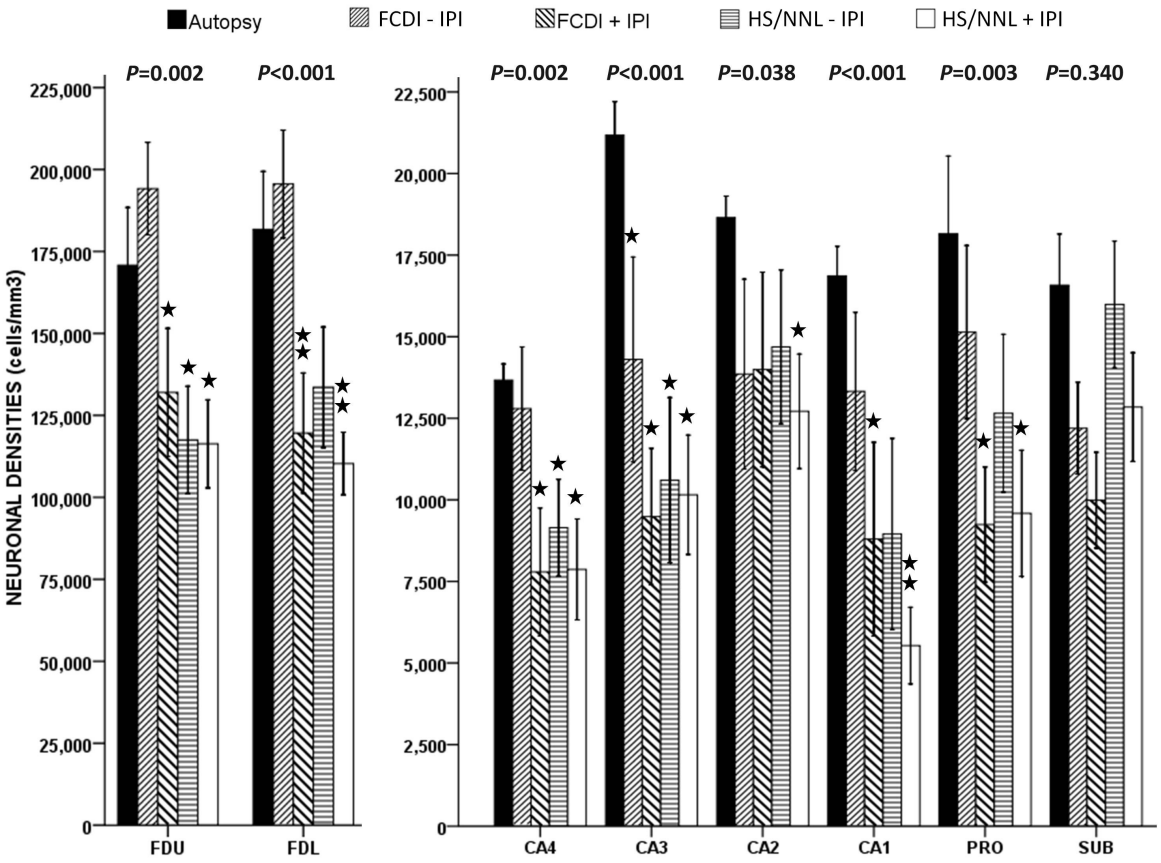

Figure 2 - Bar graphs comparing the neuronal densities (mean ± SEM) in specific subfields of hippocampal formation between Autopsy group and type I FCD patients with or without a history of an IPI (FCDI - IPI and FCDI + IPI) and HS/NNL with or without a history of an IPI (HS/NNL - IPI and HS/NNL + IPI). The pattern and amount of hippocampal neuron loss in type I FCD patients with a history of IPI is similar to the pattern observed in HS/NNL group.
The ANOVA P-values are shown above each subfield and significant post-hoc differences are shown in asterisks (ANOVA Games-Howell test). In FDU, the cell densities in both HS/NNL groups and in FCDI plus IPI group were lower than in FCDI without IPI, but similar to Autopsy. In FDL, the densities were lower in FCDI plus IPI and HS/NNL plus IPI when compared with Autopsy and FCDI without IPI, but similar to HS/NNL without IPI. In CA4, the neuronal densities in FCDI plus IPI group and both HS/NNL groups were lower than Autopsy and similar to FCDI without IPI patients. In CA3, all patients had similar neuronal densities, all lower than Autopsy cases. In CA2, the neuronal densities were lower in HS/NNL plus IPI than Autopsy, but similar to FCD without IPI, FCDI plus IPI and HS/NNL groups. In CA1, the neuronal densities were lower in HS/NNL plus IPI than Autopsy and FCDI without IPI, FCDI plus IPI had lower densities than Autopsy group. In prosubiculum (PRO), FCD plus IPI and HS/NNL plus IPI had lower neuronal densities when compared with Autopsy.

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