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# MALFORMAÇÕES DO DESENVOLVIMENTO CORTICAL:

## Contribuição dos fatores genéticos e ambientais para sua etiologia, aspectos clínicos e de neuroimagem

Tese de Doutorado apresentada à Pós-Graduação em Ciências Médica da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do título de Doutor em Ciências Médicas. Área de concentração: Neurologia.

Orientadora: Prof. Dra. Marilisa M. Guerreiro

Co-Orientador: Prof. Dr. Fernando Cendes

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*SUMÁRIO*

## *LISTA DE TABELAS*

## *LISTA DE ABREVIATURAS*

AH – Atrofia hipocampal

DCF – Displasia cortical focal

DAE – Droga antiepiléptica

EEG – eletroencefalograma

FLAIR – Fluid attenuation inversion recovery

HLS – Heterotopia laminar subcortical

MDC – Malformações do desenvolvimento cortical

PET – Tomografia por emissão de positrons

RM – Ressonância magnética

SLG – Síndrome de Lennox-Gastaut

SNC – Sistema nervoso central

## *RESUMO*

A evolução na qualidade e definição dos exames de neuroimagem possibilitou o diagnóstico das malformações do desenvolvimento cortical (MDC) ainda *in vivo*. A identificação dos diversos tipos de MDC, antes somente possível nos exames *post-morten* e o conseqüente avanço na classificação desses distúrbios, proporcionou uma melhor compreensão da sua etiologia, quadro clínico e aspectos de neuroimagem. Entretanto, ainda há muito a ser esclarecido. Neste estudo avaliamos a contribuição dos fatores genéticos e ambientais para a gênese das MDC, além dos aspectos clínicos e de neuroimagem desta entidade.

O diagnóstico das MDC foi baseado nos achados de ressonância magnética de alta resolução e do resultado do pós-processamento das imagens. Os pacientes e familiares foram entrevistados segundo um questionário semi-estruturado contendo informações sobre história familiar, epilepsia, idade da primeira crise e ocorrência de eventos pré-natais.

Para a análise dos dados, dividimos as MDC em três grupos conforme os três eventos fundamentais do desenvolvimento cortical: proliferação/apoptose celular (hemimegalencefalia e displasia cortical focal), migração neuronal (lissencefalia, heterotopia laminar subcortical e heterotopias nodulares) e organização cortical (polimicrogiria e esquizencefalia).

Esta tese foi dividida em capítulos conforme os três principais temas abordados.

Concluímos que:

**a) Sobre a influência de fatores genéticos e pré-natais na gênese das MDC:**

• MDC associadas à proliferação/apoptose anormal estão menos associadas à influências genéticas ou ambientais;

• MDC associadas à migração neuronal anormal estão freqüentemente associadas à predisposição genética;

• MDC associadas à organização cortical anormal apresentam maior associação com eventos pré-natais detectáveis, além de também apresentar predisposição genética importante;

• A idade da primeira crise epiléptica é antecipada quando há história familiar de epilepsia;

**b) Sobre o espectro clínico e eletrencefalográfico das MDC:**

• Apesar das MDC estarem muitas vezes presente em pacientes com comprometimento neurológico grave, este diagnóstico deve ser considerado mesmo quando o exame neurológico e EEG forem normais, assim como na ausência de epilepsia;

• A maioria dos pacientes com MDC associadas à proliferação ou migração anormais apresentam epilepsia refratária;

• MDC associadas à organização cortical anormal apresentam freqüência menor de epilepsia e, quando presentes, as crises epilépticas são mais facilmente controladas;

• Síndromes epilépticas secundariamente generalizadas (síndrome de West e síndrome de Lennox-Gastaut) podem estar associadas a lesões focais ou difusas, entretanto, são mais freqüentes quando a MDC é difusa;

• Polimicrogiria parietal posterior representa um subtipo "benigno" da síndrome perisylviana, caracterizando-se por atraso de fala ou disartria leve;

• Polimicrogiria é uma alteração estrutural freqüentemente associada a distúrbio específico da linguagem;

**c) Sobre os aspectos de neuroimagem das MDC:**

• O avanço das técnicas de neuroimagem permitiu a visualização de aspectos normais do cérebro, antes não observados nos exames de rotina. Desse modo determinamos que uma linha isointensa ao córtex pode ser observada próxima ao trígono, bilateralmente, nas imagens em T1. Este é um achado normal que não deve ser confundido com heterotopia laminar subcortical;

• Técnicas de pós-processamento da imagem (reconstrução multiplanar e reformatação curvilinear) melhoram a identificação e localização de lesões sutis, normalmente não observadas na inspeção visual dos filmes de ressonância magnética;

• Atrofia hipocampal está presente em 14% dos pacientes com MDC focais. Aumento do volume do hipocampo está presente em 44% dos pacientes com MDC difusas. Como a lesão hipocampal sempre é ipsilateral à lesão displásica, acreditamos que em alguns casos as duas lesões apresentam a mesma etiologia.

# 1. INTRODUÇÃO

Após o fechamento do tubo neural e da formação das vesículas telencefálicas, desenvolvimento cortical é o principal processo na formação do sistema nervoso central (SNC; Barth, 1987). O desenvolvimento do córtex cerebral humano pode ser dividido em três estágios: a) **proliferação/apoptose** das células precursoras e formação de neuroblastos ou células da glia; b) **migração** neuronal desde a matriz germinal até o córtex em desenvolvimento; e, c) **organização** cortical em seis camadas (Barkovich *et al*, 2001).

O processo de formação cortical é dinâmico e mais de um estágio pode co-existir simultaneamente. Como regra geral, o período de proliferação ocorre da $5^a/6^a$ até a $16^a/20^a$ semanas de gestação; migração a partir da $6^a/7^a$ até a $20^a/24^a$ semanas, e organização da $16^a$ até aproximadamente a $24^a$ semana gestacional (Rakic, 1988). Entretanto, existem evidências que parte da migração e organização podem ocorrer durante o terceiro trimestre da gestação (Wyllie *et al*, 1996; Inder *et al*, 1999).

A evolução na qualidade e definição dos exames de neuroimagem possibilitou a realização do diagnóstico das malformações do desenvolvimento cortical (MDC) ainda *in vivo*. Ressonância magnética (RM) e, mais recentemente, técnicas de pós-processamento da imagem possibilitaram a identificação de alterações sutis da arquitetura cortical antes não identificadas pelos exames de tomografia computadorizada ou mesmo pelos aparelhos de RM de 0,5 e 1,0 Tesla.

A identificação dos pacientes com MDC proporcionou grande avanço no entendimento da sua etiologia, assim como das suas características clínicas e de neuroimagem. Entretanto, vários aspectos ainda não foram completamente elucidados.

# 2. REVISÃO DA LITERATURA

## CLASSIFICAÇÃO

Consideramos a classificação proposta por Barkovich *et al* (2001) baseada nos três eventos embriológicos fundamentais para a formação cortical: a) **proliferação/apoptose** celular; b) **migração** neuronal; e c) **organização** cortical (Tabela 1).

### Displasia cortical focal

Displasia cortical focal (DCF) é caracterizada por desorganização focal da laminação cortical, associada a neurônios bizarros (neurônios displásicos) e células com volume aumentado e citoplasma eosinofílico (células em balão; Taylor *et al*, 1971). Podem ser evidenciadas por exames de neuroimagem como áreas de espessamento cortical, borramento entre a substância branca e cinzenta, atrofia focal e sinal hiperintenso nas seqüências T2/FLAIR. Sua etiologia ainda não foi esclarecida, e apesar de não haver casos familiares de DCF descritos na literatura, este tipo de MDC pode estar associado a doenças geneticamente determinadas como, por exemplo, esclerose tuberosa.

Estas lesões displásicas apresentam epileptogenicidade intrínseca e os pacientes são neurologicamente normais, exceto por apresentarem epilepsia parcial refratária (Palmini *et al*, 1991a; Palmini *et al*, 1995).

Atualmente, DCF é dividida em 2 subtipos: DCF com células em balão (tipo Taylor) e DCF sem células em balão (Barkovich *et al*, 2001). Como ainda há controvérsias a respeito desta classificação optamos por classificar DCF como uma MDC secundária a proliferação/apoptose celular anormal.

**Hemimegalencefalia**

Hemimegalencefalia representa a MDC que acomete um hemisfério cerebral. Ela é visualizada nos exames de neuroimagem como hipertrofia hemisférica, muitas vezes associada à dilatação ventricular. Além do aumento de volume hemisférico, pode-se encontrar áreas de paquigiria, polimicrogiria, heterotopia e gliose da substância branca subjacente (Townsend *et al*, 1975; Manz *et al*, 1979). Sua etiologia ainda não foi definida, mas pode estar associada a síndromes neurocutâneas como neurofibromatose tipo I e hipomelanose de Ito.

Clinicamente os pacientes apresentam epilepsia de difícil controle desde os primeiros meses de vida, associada a retardo do desenvolvimento neuropsicomotor, com déficit motor contralateral à lesão displásica. Apesar de um dos hemisférios ser sadio, o "bombardeamento" contínuo por descargas epilépticas provenientes do hemisfério doente pode provocar disfunção cerebral bilateral.

**Heterotopia nodular periventricular**

Heterotopia nodular periventricular é caracterizada por agrupamentos de neurônios heterotópicos próximos à matriz germinal, na região periventricular. Constitui-se de neurônios maduros e células da glia, sem organização laminar definida, formando massas com protrusão para a luz ventricular (Barth, 1987). Caracteriza-se, na maioria das vezes, por nódulos periventriculares distribuídos de forma simétrica por toda a parede ventricular, bilateralmente. Ocorre geralmente em famílias, e predomina no sexo feminino. Seu padrão

de herança já foi determinado com sendo ligado ao X; e recentemente, mutação no gene *FLN 1* foram encontradas em vários pacientes (Eksioglu *et al*, 1996; Fox *et al*, 1998).

**Heterotopia nodular unilateral**

Heterotopia nodular unilateral caracteriza-se por nódulos de substância cinzenta heterotópica, que podem variar em número e tamanho, geralmente na região peritrigonal posterior (zona de fronteira vascular), podendo estender-se em direção à substância branca, envolvendo o neocórtex adjacente. Acredita-se que não esteja associada à história familiar ou predomínio sexual, mas sim a eventos pré-natais que possam provocar injúria tecidual por falha perfusional nas zonas de fronteira vascular (Raymond *et al*, 1994).

**Lissencefalia (ou complexo agiria / paquigiria) e heterotopia laminar subcortical (ou duplo córtex)**

Lissencefalia e heterotopia laminar subcortical (HLS) representam extremos dentro do espectro de uma mesma entidade.

Na lissencefalia o cérebro apresenta número reduzido de sulcos e giros, o que resulta em sulcos rasos e giros grandes com córtex espessado. Existem vários graus de lissencefalia, desde formas leves, onde o número de sulcos e giros, apesar de diminuído, permite que o paciente apresente função cognitiva e motora compatível com vida independente, desde que supervisionada; até formas extremamente graves, com ausência completa de sulcos e giros, onde o paciente praticamente não contactua com o meio.

A etiologia da lissencefalia já foi identificada em alguns casos como sendo resultado de mutação envolvendo os genes *LIS 1* ou *DCX* (Dobyns *et al*, 1993; Dobyns *et al*, 1996; Gleeson *et al*, 1998; des Portes *et al*, 1998; Clark & Noebels, 1999). Mutação no gene *LIS1* provoca lissencefalia com predomínio nas regiões posteriores do cérebro. Nos casos onde a mutação ocorre no gene *DCX* (com herança ligada ao X) ocorre predomínio nas regiões anteriores do cérebro. Como a mutação no gene *DCX* acomete o cromossomo X, as mulheres tendem a apresentar a forma mais leve da doença, ou seja heterotopia laminar subcortical, e os homens apresentam quadro mais grave, ou seja lissencefalia (agiria/paquigiria) propriamente dita (des Portes *et al*, 1998).

HLS caracteriza-se pela ocorrência de neurônios heterotópicos, dispostos na forma de banda contínua, ou semicontínua, abaixo do manto cortical, produzindo a aparência de um córtex duplo (Palmini *et al*, 1991b). Muitos casos estão associados a mutações no gene *DCX* e raramente no gene *LIS1* (des Portes *et al*, 1998; Gleeson *et al*, 1998).

Clinicamente caracteriza-se por epilepsia e déficit cognitivo em graus variados, proporcional à espessura da banda. Quanto maior a banda heterotópica, mais grave será o comprometimento neurológico (Palmini *et al*, 1991b).

**Polimicrogiria**

Polimicrogiria é uma anomalia do desenvolvimento cortical onde os neurônios atingem o córtex cerebral, mas estão distribuídos de maneira anormal, resultando na formação de múltiplos giros pequenos. Com base em estudos anatomopatológicos, duas

formas de polimicrogiria são reconhecidas: uma onde existe estratificação em quatro camadas (*four-layered*) e outra sem esta estratificação (*unlayered*).

O tipo histológico da polimicrogiria depende da época em que insulto ocorreu. Polimicrogiria sem estratificação em camadas (*unlayered*) provavelmente decorre de falência circulatória que ocorre mais precocemente durante a gestação do que a polimicrogiria em quatro camadas (Barth, 1987; Van Bogaert *et al*, 1996). Os dois tipos de polimicrogiria podem coexistir em áreas contíguas corticais, indicando que esses dois tipos de córtex podem fazer parte de um mesmo espectro (Shevell *et al*, 1992; Guerrini & Carrozzo, 2001).

Clinicamente as polimicrogirias podem estar associadas a déficit focal variável, conforme a área cortical envolvida. Alguns pacientes podem ser praticamente assintomáticos. Uma das formas clássicas de polimicrogiria consiste no envolvimento bilateral da região perisylviana, produzindo quadro pseudobulbar e distúrbios da fala, caracterizando a síndrome perisylviana bilateral (Kuzniecky *et al*, 1993) que pode recorrer em famílias (Guerreiro *et al*, 2000).

**Esquizencefalia**

Esquizencefalia é caracterizada por uma fenda que comunica a superfície cortical com a luz ventricular. Nas suas bordas existe tecido cortical anormal (polimicrogiria). Quando suas bordas estão justapostas denomina-se esquizencefalia de lábios fechados; e quando suas bordas estão afastadas, denomina-se esquizencefalia de lábios abertos.

A etiologia das esquizencefalias ainda não foi totalmente esclarecida. Acredita-se que um insulto vascular durante o desenvolvimento cortical, pode provocar o desenvolvimento desta MDC. Barkovich & Kjos (1992) sugerem que a injúria cortical superficial resultará em polimicrogiria; e uma lesão mais grave que se estende profundamente no hemisfério e destrói completamente as fibras radiais gliais resultará em esquizencefalia. Ainda, a destruição parcial das fibras radiais gliais resultará em invaginamento cortical e polimicrogiria.

Surpreendentemente, estudos moleculares de casos com recorrência familiar (além de alguns casos isolados) demonstraram a presença de alterações no gene homeobox *EMX2* em alguns pacientes (Granata *et al*, 1997).

O quadro clínico de pacientes com esquizencefalia pode ser variado, e muitas vezes observa-se déficit motor focal contralateral à lesão, além de epilepsia.

## GENÉTICA

Aspectos genéticos determinam a distribuição dos neuroblastos em camadas e regiões específicas. Genes regulatórios "homeobox" (que controlam a formação de compartimentos anatômicos específicos) regulam os vários estágios da formação do SNC, participando, por exemplo, da segmentação do cérebro em prosencéfalo, mesencéfalo, rombencéfalo e seus constituintes. Outros regulam a síntese de proteínas de adesão que controlam o contato dos neuroblastos entre si e com as fibras radiais gliais ao longo do processo de migração e formação das sinapses (Palmini,1996).

MDC podem estar associadas a doenças ou síndromes geneticamente determinadas (Tabela 2; Barkovich, 1996b). Um exemplo é a ocorrência de lissencefalia na síndrome de Miller-Diecker (Reiner *et al*, 1993; Dobyns *et al*, 1996).

Um dos maiores avanços na elucidação do mecanismo molecular associado às MDC ocorreu no grupo das lesões causadas por migração neuronal anormal (Tabela 3). Após a descoberta de mutações nos genes *LIS1* e *DCX,* lissencefalia (complexo agiria/paquigiria) e HLS passaram a ser classificadas como extremos dentro do espectro de uma mesma condição (Reiner *et al*, 1993; Dobyns *et al*, 1993; Gleeson *et al*, 1998; des Portes *et al*, 1998; Clark *et al*, 1999).

Pacientes com mutação no gene *LIS1* podem apresentar fenótipo variado, com lissencefalia difusa, paquigiria posterior ou HLS com predomínio nas regiões posteriores. A mutação no gene *DCX* produz fenótipo mais variado ainda, desde lissencefalia (agiria/paquigiria) até HLS parcial (Barkovich *et al*, 2001).

Formas familiares de heterotopia nodular periventricular bilateral também já foram descritas. Mutações no gene *FLN1* foram identificadas nesses pacientes, sendo que tal gene é ligado ao cromossomo X (Fox *et al*, 1998). A caracterização genética destas entidades é muito importante; pois, o espectro clínico destas patologias pode ser muito heterogêneo entre diferentes indivíduos de uma mesma família. Clinicamente os pacientes podem apresentar desde comprometimento neurológico grave com deficiência mental e epilepsia de difícil controle, até epilepsia facilmente controlada por drogas antiepilépticas e inteligência normal. O polimorfismo fenotípico dificulta a identificação dos pacientes afetados e a triagem molecular pode ser utilizada como ferramenta importante na investigação destes pacientes e de seus familiares.

Mutação no gene *EMX2* foi descrita em pacientes com esquizencefalia. Como outros genes que codificam fatores de transcrição, o *EMX2* atua como um gene regulatório, e o seu análogo em ratos é expresso especificamente em neuroblastos em proliferação (Brunelli *et al*, 1996; Granata *et al*, 1997). Entretanto, nem todos os pacientes com esquizencefalia apresentam esta mutação, e como estes achados ainda não foram reproduzidos por outros grupos, existem controvérsias a respeito desse assunto. Nos casos sem origem genética definida um insulto vascular local durante o desenvolvimento cortical poderia estar envolvido na sua patogênese. Citomegalovirose também pode estar associada à gênese da esquizencefalia, através de falha perfusional seguida por vasculite, instabilidade hemodinâmica transitória ou lesão lítica na região da matriz germinal (Iannetti *et al*, 1998).

Recentemente, 12 famílias com mais de um indivíduo apresentando síndrome perisylviana foram descritas (Guerreiro *et al*, 2000). Os achados sugerem herança ligada ao X na maioria das famílias, enquanto em outras, a herança parece ser autossômica dominante.

Apesar de algumas famílias apresentarem história familiar de MDC (sugerindo uma forte determinação genética), a determinação do padrão de herança genética ou mutação específica ainda não foi estabelecida em todos os subtipos de MDC.

## FATORES AMBIENTAIS

Além da determinação genética, fatores ambientais e intercorrências gestacionais parecem contribuir para a patogênese das MDC. Alguns estudos relatam a concomitância de eventos pré-natais que podem ter determinado, e a ocorrência de malformação cortical (Landrieu & Lacroix, 1994; Palmini *et al*, 1994; Van Bogaert *et al*, 1996). Entretanto, existem poucos trabalhos que estudaram sistematicamente uma série grande de pacientes. Palmini *et al* (1994) avaliaram a freqüência de intercorrências pré-natais em 40 pacientes com MDC, comparando-os a pacientes epilépticos sem MDC. Os autores concluíram que eventos pré-natais potencialmente nocivos provavelmente participam da patogênese das MDC. Kuzniecky *et al* (1993) relatam a ocorrência de gestação com intercorrências em apenas 6 pacientes de um grupo de 31 crianças com polimicrogiria perisylviana bilateral. Entretanto, apesar da metodologia adequada, acreditamos que o questionamento ativo durante o decorrer de mais de uma consulta, com interrogatório dirigido e sistemático poderia revelar dados mais significativos.

A maioria dos outros estudos apresenta relatos anedóticos, entre eles, destaca-se a ocorrência de polimicrogiria em gêmeo monozigótico que havia sofrido transfusão feto-fetal durante a gestação. O gêmeo sem intercorrências clínicas pré-natais não apresentava malformação do SNC, portanto, fatores como hipotensão arterial e hipovolemia podem ter contribuído na fisiopatologia do quadro (Sugama & Kusano, 1994). Outro caso entre gemelares monozigóticos mostra a ocorrência de polimigrogiria perisylviana bilateral em um dos gêmeos, com morte do outro gemelar. Neste caso foi documentada isquemia

intrauterina por transfusão feto-fetal, com morte do gêmeo doador entre a 16ª e 18ª semanas de gestação (Van Bogaert *et al*, 1996).

A alta incidência de lesões displásicas bilaterais na região perisylviana tem sido usada como evidência de que provavelmente o mecanismo lesional envolva hipotensão sistêmica fetal com isquemia cortical bilateral, seja por acometimento do território irrigado pela artéria cerebral média, ou por isquemia localizada em zonas de fronteira vascular.

Esquizencefalia e polimicrogiria representam diferentes extremos dentro do espectro de uma mesma entidade: quanto mais extenso o insulto vascular, mais intensa a polimicrogiria eventualmente atingindo o epêndima ventricular, e portanto, constituindo uma fenda (esquizencefalia). A lesão cortical superficial resulta em polimicrogiria plana, sem dobras corticais. Lesões mais graves, que se estendem mais profundamente nos hemisférios e destroem as fibras radiais gliais (ou suas moléculas de superfície que promovem a migração neuronal), resultam em dobras corticais com polimicrogiria nas suas bordas. Se a lesão envolver toda a espessura do hemisfério, da pia-máter até o epêndima, forma-se a esquizencefalia (Barkovich & Kjos, 1992).

## NEUROIMAGEM

O diagnóstico *in vivo* das MDC só foi possível após o desenvolvimento de técnicas de neuroimagem. Tomografia computadorizada pode identificar lesões extensas, entretanto, a RM é o método de escolha na investigação das MDC. O aperfeiçoamento da RM com a melhora da resolução da imagem permitiu a visualização de lesões discretas, muitas vezes imperceptíveis aos exames realizados em equipamento de 0,5 Tesla. Um exemplo é a displasia cortical focal, a qual pode ser identificada apenas através de sinais sutis como uma área de borramento entre a substância branca e cinzenta, espessamento cortical ou sinal hiperintenso nas seqüências T2/FLAIR (Sisodiya *et al*, 1995; Barkovich *et al*, 1997; Li *et al*, 1998).

Algumas vezes as lesões displásicas, entretanto, podem ser muito pequenas, quase imperceptíveis à análise visual convencional dos filmes de RM. Na tentativa de solucionar este problema, técnicas de pós-processamento da imagem foram desenvolvidas. Neste estudo utilizamos três métodos de pós-processamento da imagem: volumetria, reformatação multiplanar e reconstrução curvilinear.

Volumetria é uma técnica que permite a análise quantitativa de regiões pré-determinadas. Sua comparação com os valores encontrados em controles normais permite a identificação de valores anormais, sejam eles acima ou abaixo do normal. Volumetria hipocampal foi primeiramente realizada em pacientes com epilepsia do lobo temporal e tem sido uma ferramenta importante na identificação de lesões hipocampais sutis (Cascino *et al*, 1991; Cendes *et al*, 1993a; Watson *et al*, 1996).

Reformatação multiplanar é um método interativo de análise a partir de uma aquisição volumétrica. Esta técnica permite a visualização de uma mesma região cerebral em diferentes planos, simultaneamente. Nesse estudo, a reformatação multiplanar foi realizada em uma estação de trabalho ($O_2$ Silicon Graphic) utilizando-se o software Omnipro (Elscint Prestige, Haifa, Israel). Este programa permite a reconstrução rápida das imagens de RM em qualquer plano desejado. Para melhor identificação das anormalidades, imagens T1 e T2/FLAIR foram analisadas.

Reformatação curvilinear é uma técnica que permite a diferenciação entre lesões sutis e artefato de volume parcial. A técnica foi desenvolvida para evitar a impressão de espessamento cortical observada em imagens feitas com cortes grossos de RM, devido ao plano de secção oblíquo em relação ao giro cerebral (Bastos *et al*, 1999). Nesse estudo a reformatação curvilinear foi realizada utilizando-se o software Brainsight (Rogue Research, Montreal, Quebec, Canadá). Esta técnica melhora a visualização da estrutura dos giros na convexidade hemisférica e evita a ocorrência de resultados falso positivos.

# 3. OBJETIVOS

**Nossos objetivos foram:**

a) Avaliar a influência dos fatores genéticos e pré-natais na gênese das malformações do desenvolvimento cortical.

b) Avaliar o espectro clínico e eletrencefalográfico das malformações do desenvolvimento cortical.

c) Avaliar os aspectos de neuroimagem das malformações do desenvolvimento cortical.

# 4. CAPÍTULOS

# Capítulo I

# Aspectos históricos

Artigo 1 – Focal cortical dysplasia

**Focal Cortical Dysplasia**

*Arch Neurology (History Section - Seminal Citation), in press*

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# FOCAL CORTICAL DYSPLASIA

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Focal cortical dysplasia (FCD) is a type of malformation of cortical development (MCD) that primarily affects areas of neocortex. It can be identified on conventional MRI as focal cortical thickening, abnormal gyration and blurring between gray and white matter, many times associated with clusters of heterotopic neurons. FCD is one of the most common entities associated with refractory epilepsy, especially in childhood.

**FIRST DESCRIPTION**

Taylor and colleagues [1] wrote the first clear description of FCD in their report of pathological findings of lobectomy specimens from epilepsy surgery.

> "The most striking microscopic feature at low power was the localized disruption of the normal cortical lamination by an excess of large aberrant neurons scattered randomly through all but the first layer…The aberrant nerve cells stood out partly because of their numbers and their inappropriate size, which at times approached that of a giant Betz cell, and partly because of their bizarre structure.[1]"

They acknowledged that the pathological appearance of FCD resembled Crome's [2] description of localized cerebral gliosis, characterized by giant nerve cells and disrupted cortical lamination. In fact, Crome's report might have been the first description of FCD, 14 years before Taylor's work.[2]

## *FORME FRUSTE* OF TUBEROUS SCLEROSIS

Before Taylor, few authors had described epilepsy associated with giant nerve cells and disrupted cortical architecture. Although these reports lacked evidence of multiple cerebral lesions, periventricular nodules or multiple organ involvement, the pathological resemblance to cellular changes in tuberous sclerosis was always mentioned .[2,3] For many decades, FCD was considered as a *forme fruste* of tuberous sclerosis.

> "The lack of so many of the remarkably distinctive features of tuberous sclerosis may, however, not rule out the condition, particularly as *formes frustes* are known to occur occasionally...[1]"

Today, however, FCD is classified as an entity apart from tuberous sclerosis, and it is interesting to note that, in 1957, Crome already stated that:

> "... (giant nerve cells) are a special and familiar feature of tuberous sclerosis. They are, however, non-specific and known to be associated with other conditions, such as pachygyria.[2]"

## ETIOLOGY

Although more than 30 years have passed since Taylor's report, little is known about the etiology of FCD.

The updated classification of MCD [4] divides FCD into two different types, according to the presence or absence of balloon cells. FCD with balloon cells (Taylor-type) is considered an abnormality of neuronal and glial proliferation or apoptosis. Conversely, FCD without balloon cells is now listed in the group of MCD due to abnormal cortical organization.

> "...the absence of balloon cells suggests that the divergence from normal development occurs after the period of cell proliferation. The absence of heterotopia puts the timing after the period of neuronal migration, as well.[4]"

However, because FCD has heterotopic neurons in the white matter and that cortical development is a dynamic process where there is an overlap of one or more stages during several weeks, it is likely that all three stages of cortical development – cellular proliferation/apoptosis, neuronal migration and cortical organization – are involved in its pathogenesis.

## ROLE OF HEREDITARY *versus* ENVIRONMENTAL PRECIPITANTS

There is no description of familial cases FCD, and its molecular basis has not been defined. However, the fact that FCD can be associated with specific neurological syndromes suggests that genetics probably play a role in its pathogenesis. FCD without balloon cells may represent the result of localized prenatal cortical injury. [4]

> "...these cortical dysplasias (FCD without balloon cells) have the appearance of a localized prenatal injury, suggesting that prenatal infarction or infection after neuronal migration might alter the local effects on cell maturation and result in the development of giant, dysplastic-appearing cells.[4]"

## CLINICAL SIGNS and EEG

In 1971, Taylor already linked the pathological findings directly to the clinical signs of epilepsy:

> "For the present, therefore, it would seem best to look on these abnormalities as a particular form of localized cortical dysplasia in which anomalous populations of neurons, and often of glia, underlie the electrical and clinical manifestations of certain focal forms of epilepsy. [1]"

Patients with FCD are usually intellectually normal, and with few exceptions, present refractory epilepsy. One of the major advances in the history of FCD was the description of its electroencephalographic pattern – characterized by very frequent, almost continuous, epileptiform activity – as well as its unique property of intrinsic epileptogenicity [5, 6] (Figure).

## DIAGNOSIS

In the past, the diagnosis of FCD was performed through pathological examination of specimens resected, during electrocorticography-guided surgery, from patients with refractory epilepsy. [1] Advances in neuroimaging enabled the *in vivo* diagnosis of dysplastic areas. Magnetic resonance imaging (MRI) has been the most important tool for the diagnosis of FCD.

Today, the neuroimaging characteristics of FCD are well established and its diagnosis can be achieved with confidence based on imaging findings (Figure). MRI is more sensitive than computerized tomography because of its better contrast between gray and white matter[7]. More recently, positron emission tomography and image post-processing techniques enabled the identification of subtle dysplastic lesions in patients with "cryptogenic" epilepsy. [8-10]

## TREATMENT

Since its first description, FCD has been associated with refractory epilepsy. The treatment should be aimed toward optimal seizure control, and the type of antiepileptic drug depends on the seizure subtype, which may vary according to the patient's age. When treatment with antiepileptic drug fails, epilepsy surgery should be considered.

However, despite the development of new antiepileptic drugs and the improvement in surgical techniques, seizure control remains a challenge in patients with FCD.

For several decades, epilepsy surgery has been the treatment of choice for refractory epilepsy associated with defined lesions. From a historical perspective, whereas, FCD was present in only 3% (10/300 patients) of Taylor's surgical series,[1] today, FCD is frequently diagnosed and is one of the most common causes of refractory seizures that require surgical treatment. In fact, in current reports, cortical malformation (mostly FCD) are present in approximately 20%-30% of the specimens reported at epilepsy surgery. [11] It is believed that, in children, these numbers may be even higher.

**ACNKOWLEDGEMENTS**

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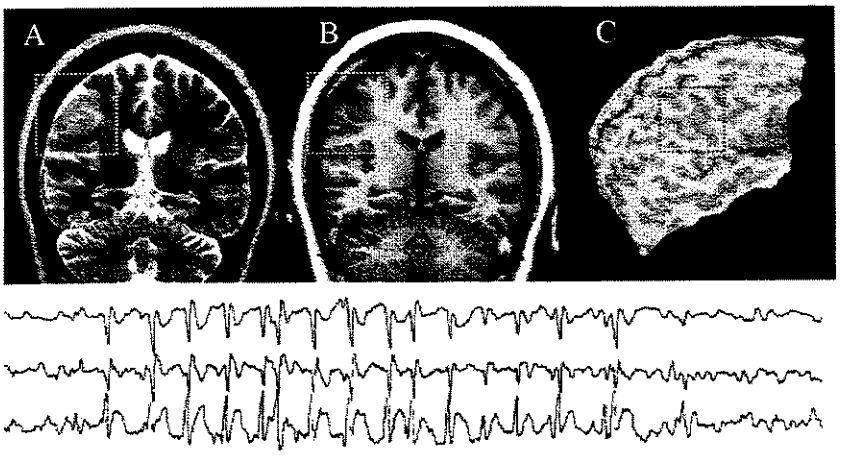


**Figure 1** – Upper row: A and B - Coronal T2 and T1-IR images showing an area of abnormal gyration, focal cortical thickening, blurring between the gray and white mater, and heterotopic neurons lining between the cortex and ventricular walls (box). C - Curvilinear reformation at 12 mm from the cortical surface showing an area of focal cortical dysplasia (box). Bottom row: scalp EEG from a patient with focal cortical dysplasia showing very frequent, almost continuous epileptiform activity.

# Capítulo II

## Influência de fatores genéticos e pré-natais na gênese das MDC

Artigo 2 – Interrelationship of genetics and prenatal injury in the genesis of malformations of cortical development

Artigo 3 – Family history of epilepsy is associated with earlier seizure onset in patients with focal cortical dysplasia

**Interrelationship of Genetics and Prenatal Injury in the Genesis of Malformations of Cortical Development**

*Arch Neurol 2002; 59:1147-1153.*

ORIGINAL CONTRIBUTION

# Interrelationship of Genetics and Prenatal Injury in the Genesis of Malformations of Cortical Development

*Maria Augusta Montenegro, MD; Marilisa M. Guerreiro, MD, PhD; Iscia Lopes-Cendes, MD, PhD; Carlos A. M. Guerreiro, MD, PhD; Fernando Cendes, MD, PhD*

**Context:** Although the causes of some malformations of cortical development (MCD) have been established, others remain unclear. There are several lines of evidence supporting the theory of a complex mechanism that involves genetic and environmental factors.

**Objective:** To investigate the interrelationship of genetics and prenatal injury in the genesis of MCD.

**Patients and Design:** A series of 76 consecutive patients with MCD and their families were systematically questioned about their family histories of epilepsy or other neurological impairment and the occurrence of prenatal events. Whenever possible, magnetic resonance imaging was performed in other family members if MCD was suspected or in the presence of any neurological impairment. Patients were divided into 3 groups according to the type of MCD. Patients in group 1 had focal cortical dysplasia, group 2 had heterotopias (periventricular or subcortical) or agyria-pachygyria, and group 3 had polymicrogyria or schizencephaly. These findings were also compared with a disease-control group of 40 consecutive patients with epilepsy but without MCD.

**Setting:** Neurology clinic of a university hospital.

**Results:** Of the 76 patients with MCD, 21 (28%) had focal cortical dysplasia, 19 (25%) had heterotopias or agyria-pachygyria, and 36 (47%) had polymicrogyria or schizencephaly. There were 39 men and 37 women, aged 2 to 52 years (mean age, 13 years). In group 2, 6 patients (32%) had a family history of MCD, mental retardation, or miscarriages, suggesting a genetic predisposition. In group 3, family history of MCD was present in 5 patients (14%). Prenatal events occurred in 28 patients with MCD (37%) and 2 controls (5%) and were more frequent in patients with heterotopia or agyria-pachygyria and polymicrogyria ($P < .001$). Conversely, epilepsy occurred in all patients in group 1, in 17 patients (89%) in group 2, and in 17 patients (47%) in group 3. In group 3, epilepsy was less frequent ($P < .001$) and also more easily controlled ($P = .005$) than in other forms of MCD.

**Conclusions:** Our findings support the idea of a spectrum among the different types of MCD. Focal cortical dysplasia (group 1) is associated with more frequent and severe epilepsy and less important genetic and prenatal events, heterotopias and agyria-pachygyria (group 2) are frequently associated with genetic predisposition, and polymicrogyria and schizencephaly (group 3) are less frequently associated with epilepsy but have a stronger association with genetic and detectable prenatal events.

*Arch Neurol. 2002;59:1147-1153*

*From the Departments of Neurology (Drs Montenegro, M. Guerreiro, C. Guerreiro, and Cendes) and Medical Genetics (Dr Lopes-Cendes), University of Campinas, Campinas, Brazil.*

THE MIGRATION of neuroblasts from the periventricular germinal matrix to their final destination and their organization within the cortical mantle may be disturbed by genetic or environmental factors.[1-15] The interrelationship of genetics and prenatal events as contributors to malformations of cortical development (MCD) has been reported previously. However, few studies of large series are available.[2,4]

The objective of this study was to investigate the occurrence of genetic predisposition and prenatal events and the interaction between these factors in a large series of patients with different types of MCD. We believe that this study may clarify the complex mechanisms involved in normal and abnormal cortical development.

## RESULTS

### DISEASE-CONTROL GROUP

Of 40 control subjects with epilepsy, 32 (80%) had temporal lobe epilepsy, 3 (8%) had frontal lobe epilepsy, and in 5 (13%) the localization was not established. The

## PATIENTS AND METHODS

This study was conducted at the neurology clinic of a university hospital. We evaluated 76 consecutive patients with a diagnosis of MCD confirmed by high-resolution magnetic resonance imaging (MRI). All patients were examined by at least 1 of us, and, whenever possible, an MRI was performed in other family members if cortical maldevelopment was suspected. We systematically investigated all patients and family members with any neurological disturbance, even when symptoms were mild, such as speech delay in early childhood. All patients signed an informed consent form approved by the ethics committee of the University of Campinas, Campinas, Brazil.

We used a semistructured questionnaire to ask patients and their families about family history of epilepsy or other neurological impairment in first-degree, second-degree, or third-degree relatives and the occurrence of any prenatal event during the first 24 weeks of gestation. Significant prenatal events included any abnormality reported by the mother or family during the first 24 weeks of gestation, such as a failed abortion attempt, drug addiction, physical abuse, a fall with abdominal trauma, hypertension, fever, skin rash, diabetes mellitus, exposure to x-rays, twin gestation, cytomegalovirus infection, and tonic-clonic seizure. Vaginal bleeding was not included as a significant prenatal event in this study because it is difficult to establish if the bleeding had any repercussion that led to vascular injury, such as in placental anomalies, or was already the result of a major malformation. In addition, we did not include the use of over-the-counter medications as a risk factor because, even though they are often used in the first 24 weeks of gestation, these drugs have not been associated with the pathogenesis of MCD. Because the occurrence of a prenatal event was retrospectively assessed, we directly interviewed the patients' mothers and other available family members. In addition, we reviewed the clinical files of all patients.

The diagnosis of MCD was established according to MRI findings. The MRI was performed with a 2.0 T scanner (Elscint Prestige; Elscint Ltd, Haifa, Israel), using our epilepsy protocol: (1) sagittal T1-weighted spin-echo, 6 mm thick (repetition time [TR], 430; echo time [TE], 12) for optimal orientation of the subsequent images; (2) coronal T1 inversion recovery, 3 mm thick (flip angle, 200°; TR, 2800-3000; TE, 14; inversion time [TI], 840; matrix, 130×256; field of view [FOV], 16×18 cm); (3) coronal T2-weighted fast spin-echo, 3 to 4 mm thick, (flip angle, 120°; TR, 4800; TE, 129; matrix, 252×320; FOV, 18×18 cm); (4) axial images parallel to the long axis of the hippocampus; T1 gradient echo, 3 mm thick (flip angle, 70°; TR, 200; TE, 5; matrix, 180×232; FOV, 22×22 cm); (5) axial T2 fast spin-echo, 4 mm thick (tip angle, 120°; TR, 6800; TE, 129; matrix, 252×328; FOV, 21×23 cm); and (6) volumetric (3-dimensional) T1 gradient echo, acquired in the sagittal plane for multiplanar reconstruction, 1 to 1.5 mm thick (tip angle, 35°; TR, 22; TE, 9; matrix, 256×220; FOV, 23×25 cm). We performed multiplanar reconstruction and curvilinear reformatting in all 3-dimensional MRIs.[16]

Patients were divided into 3 groups according to the MRI findings of MCD. Patients in group 1 had focal cortical dysplasia, group 2 had heterotopias (periventricular or subcortical) or agyria-pachygyria, and group 3 had polymicrogyria or schizencephaly (**Figure 1**).

We also assessed a disease-control group and performed detailed interviews about the occurrence of prenatal events and family history of any neurological disturbance. The same semistructured questionnaire was used for patients with MCD and controls. The disease-control group consisted of 40 consecutive patients with epilepsy seen prospectively at our epilepsy clinic (26 women; age range, 6-54 years; mean age, 26.9 years) who underwent neuroimaging evaluation according to our epilepsy protocol and whose MRI findings excluded the presence of MCD. We excluded patients with major destructive lesions, such as porencephaly or hemispheric atrophy.

We used the $\chi^2$ test to analyze differences in the frequency distribution of prenatal events, family history of epilepsy, family history of neurological impairment, and occurrence of epilepsy and seizure control among the different groups of patients with MCD and the control group, when appropriate. A $P$ value of less than .05 was considered significant.

cause of epilepsy according to MRI findings was hippocampal sclerosis in 16 patients (40%), cavernous angioma in 3 (8%), low-grade tumor in 3 (8%), gliosis in 2 (5%), and cysticercosis in 2 (5%); 14 patients had normal findings on MRI. Family history of epilepsy was present in 13 patients (33%), mental retardation in 1 patient (3%), and history of miscarriage in 1 patient (3%). Two patients (5%) had a history of prenatal events during pregnancy. One reported fever in the first trimester of pregnancy, and the other reported amniotic bands, with multiple finger amputation.

### PATIENTS WITH MCD

We evaluated 76 patients, 39 men and 37 women, whose ages ranged from 2 to 52 years (mean age, 13.8 years). Twenty-one patients (28%) had focal cortical dysplasia (52% men), 19 patients (25%) had heterotopias or agyria-pachygyria (26% men), and 36 patients (47%) had polymicrogyria or schizencephaly (67% men). **Tables 1**, **2**, and **3** present the characteristics of patients in each group. **Figure 2** shows the frequency of prenatal events, epilepsy, family history of neurological impairment, and family history of epilepsy, according to each group.

Patients in group 1 (Table 1; focal cortical dysplasia) had a lower frequency of prenatal events (5 [24%]) and family history of neurological impairment (3 [14%]) than the other 2 groups of patients with MCD and the disease-control group ($P$=.002). None of the patients in group 1 had a family history of MCD.

In group 2 (heterotopias or agyria-pachygyria), 8 patients (42%) had a history of a prenatal event that may have contributed to the pathogenesis of MCD (Table 2; patients 1-4, 7, 8, 11, and 14). Six patients (32%) had familial occurrence of MCD, mental retardation, or mis-

carriages, suggesting a genetic predisposition (Table 2; patients 1, 7, 9, and 11-13).

In group 3 (polymicrogyria or schizencephaly), 15 patients (42%) had a history of a prenatal event (Table 3; patients 1-15). Five patients (14%) had a family history of MCD in a first-degree relative (Table 3; patients 1, 18, 19, 27, and 33), and 8 (22%) had a family history of mental retardation, developmental delay, or miscarriage (Table 3; patients 5, 9-11, 20, 21, 31, and 32).

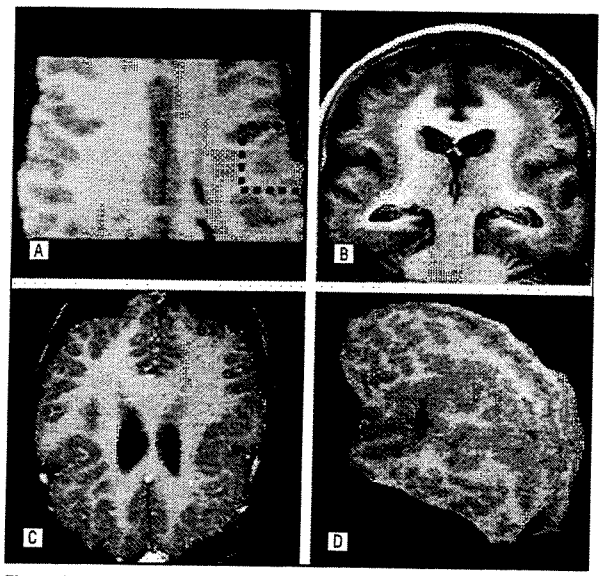


**Figure 1.** A 2-dimensional curvilinear reconstruction (A) shows a focal cortical dysplasia with thickening of the left postcentral gyrus and blurring between gray and white matter (box; Table 1, patient 6). A coronal T1 image (B) shows diffuse subcortical band heterotopia/double cortex (Table 2, patient 2). An axial T1 image (C) shows bilateral perisylvian polymicrogyria (Table 3, patient 23). A curvilinear reconstruction of the same patient as in Figure 1C (D) shows the extension of the polymicrogyria from the sylvian fissure until the parieto-occipital regions.

Family history of epilepsy was present in all groups of patients with MCD and in the disease-control group, and no significant differences in the frequency of a family history of epilepsy were detected among the groups ($P$=.18). Sixteen family members underwent MRI, and 5 (31%) had MCD (group 2, patient 13; and group 3, patients 18, 19, 27, and 33).

Epilepsy occurred in all patients with focal cortical dysplasia, and seizures were controlled with antiepileptic drugs in only 4 patients (19%). In group 2 (heterotopias or agyria-pachygyria), 17 patients (89%) had epilepsy, and only 1 (5%) had her seizures controlled with antiepileptic drugs. In group 3 (polymicrogyria or schizencephaly), 17 patients (47%) had epilepsy, and 9 of these (53%) were seizure-free after introduction of antiepileptic drugs. The frequency of epilepsy was lower ($P$<.001) and more easily controlled ($P$ = .005) in group 3.

## COMMENT

The development of human cerebral cortex can be divided into 3 overlapping stages: proliferation of stem cells into neuroblasts or glial cells, migration from the periventricular germinal matrix toward the developing cortex, and cortical organization within 6 layers associated with synaptogenesis and apoptosis.[9,17-19] This is a dynamic process, and 1 or more stages may occur simul-

**Table 1. Characteristics of Patients With Focal Cortical Dysplasia (FCD; Group 1)***

| Patient No./ Age,y/Sex | Imaging Findings | Prenatal Event | Family History (No. of Relatives) | Age at First Seizure | Clinical Outcome | Cognitive Status† |
|---|---|---|---|---|---|---|
| 1/9/F | FCD | ... | MR (1) | 3 y | Daily seizures | Normal |
| 2/6/M | FCD | Diabetes | Epilepsy (3) | 4 mo | Daily seizures | Normal |
| 3/2/M | FCD >1 lobe | ... | ... | 17 d | Weekly seizures | Mild MR |
| 4/3/F | FCD >1 lobe | ... | ... | 3 mo | Weekly seizures | Normal |
| 5/7/M | FCD | ... | Epilepsy (1) | 1.5 y | Daily seizures | Normal |
| 6/24/F | FCD | ... | ... | 10 y | Weekly seizures | Normal |
| 7/19/M | FCD | Exposure to 13 abdominal x-rays | ... | 16 y | Seizures controlled with AED | Normal |
| 8/20/M | FCD | ... | Epilepsy (1) | 12 y | Weekly seizures | Normal |
| 9/4/M | FCD | ... | Epilepsy (4) | 2 y | Daily seizures | Normal |
| 10/25/F | FCD | ... | Epilepsy (1); febrile seizure (1) | 2 y | Weekly seizures | Normal |
| 11/4/F | FCD | Twin gestation; low birth weight | Epilepsy (2) | 9 mo | Monthly seizures | Normal |
| 12/13/M | FCD | ... | ... | 6 y | Seizures controlled with AED | Normal |
| 13/29/F | FCD | ... | ... | 14 y | Weekly seizures | Normal |
| 14/16/M | FCD | ... | ... | 9 y | Daily seizures | Normal |
| 15/19/F | FCD | High blood pressure | Epilepsy (1) | 6 y | Monthly seizures | Normal |
| 16/7/M | FCD | Fever | Neonatal death (1) | 2 y | Seizures controlled with AED | Normal |
| 17/3/F | FCD | ... | Epilepsy (1) | 1 mo | Seizures controlled with AED | Normal |
| 18/4/F | FCD | ... | ... | 2 y | Daily seizures | Normal |
| 19/41/F | FCD | ... | ... | 1.5 y | Weekly seizures | Normal |
| 20/38/M | FCD | ... | ... | 22 y | Monthly seizures | Normal |
| 21/10/M | FCD | ... | Epilepsy (6); stillbirth (1) | 7 mo | Weekly seizures | Normal |

*MR indicates mental retardation; AED, antiepileptic drugs; and ellipses, not applicable.
†Cognitive status was assessed during neurological examination.

**Table 2. Characteristics of Patients With Heterotopias or Agyria-Pachygyria (Group 2)***

| Patient No./ Age, y/Sex | Imaging Findings | Prenatal Event | Family History (No. of Relatives) | Age at First Seizure | Clinical Outcome | Cognitive Status† |
|---|---|---|---|---|---|---|
| 1/12/M | Agyria/pachygyria | High blood pressure | Stillbirth (1); MR (1) | 3 mo | Daily seizures | MR |
| 2/12/F | Subcortical band heterotopia | Exposure to x-rays | Epilepsy (2) | 11 y | Daily seizures | MR |
| 3/12/F | Agyria/pachygyria | Cytomegalovirus infection | ... | 3 d | Daily seizures | MR |
| 4/4/M | Agyria/pachygyria | Fever and skin rash | Epilepsy (1) | 2 mo | Daily seizures | MR |
| 5/22/F | Subcortical band heterotopia | ... | ... | 4 y | Daily seizures | MR |
| 6/25/F | Subcortical band heterotopia | ... | Epilepsy (1) | 2.5 y | Daily seizures | MR |
| 7/28/F | Bilateral PNH | Tonic-clonic seizure in the second month | PNH (1); 5 spontaneous abortions | 4 y | Daily seizures | MR |
| 8/3/M | Agyria/pachygyria | Abortion attempt | Epilepsy (2) | 3 mo | Daily seizures | MR |
| 9/7/M | Lissencephaly | ... | Epilepsy (1); MR (1); multiple malformations (1) | 5 mo | Daily seizures | MR |
| 10/3/M | Pachygyria | ... | ... | ... | ... | MR |
| 11/10/F | Lissencephaly | Fever and skin rash | MR (6) | 2.5 y | Daily seizures | MR |
| 12/30/F | Subcortical band heterotopia | ... | MR (1) | 7 y | Weekly seizures | MR |
| 13/29/F | Bilateral PNH | ... | PNH (1); 5 spontaneous abortions | ... | ... | Normal |
| 14/34/F | Bilateral PNH | Abortion attempt | ... | 29 y | 4 seizures yearly | Normal |
| 15‡/6/F | Agyria/pachygyria | ... | ... | 1 y | Seizures controlled with AED | MR |
| 16/19/F | Subcortical heterotopia (transmantle) | ... | ... | 12 y | Daily seizures | MR |
| 17/4/F | Agyria/pachygyria | ... | ... | 2 y | Weekly seizures | MR |
| 18/52/F | Subcortical heterotopia (transmantle) | ... | ... | 36 y | 3 seizures yearly | Normal |
| 19/29/F | Pachygyria | ... | Epilepsy (1) | 9 y | Weekly seizures | MR |

*MR indicates mental retardation; PNH, periventricular nodular heterotopia; and ellipses, not applicable.
†Cognitive status was assessed during neurological examination.
‡This patient also had neurofibromatosis 1.

taneously during several weeks. As a general rule, the proliferation stage ranges from the 5th or 6th until the 16th or 20th gestational week; migration from the 6th or 7th until the 20th or 24th gestational week, and organization from the 16th until approximately the 24th gestational week.[18] There is evidence that some migration and organization could take place even during the third trimester of pregnancy.[13,20]

Normal cortical development depends on many interacting components such as trophic factors, cell-adhesion molecules, cell-cell contact-dependent signals, and possibly other currently unrecognized factors.[21] Its association with several genetically determined syndromes, such as neurofibromatosis 1, tuberous sclerosis, hypomelanosis of Ito, Walker-Warburg, Aicardi, Zellweger, Miller-Diecker, and many others, and the occurrence of familial cases of MCD (X-linked lissencephaly, subcortical-band heterotopia, schizencephaly, periventricular nodular heterotopia, and congenital bilateral perisylvian syndrome) strongly indicate a genetic component in the processes leading to different forms of MCD.[4,9,17,22] More recently, mutations in a few genes, *LIS-1* and *DCX* in lissencephaly and filamin 1 in periventricular nodular heterotopia, have been shown to cause some forms of MCD.[3,5-9,22,23] The studies by des Portes et al[10] and Gleeson et al[7,8] showed that some forms of subcortical band heterotopia and agyria-pachygyria (or lissencephaly) represent 2 different extremes within the spectrum of the same disease, which has an X-linked pattern of inheritance.

There are several reports indicating that harmful prenatal events are likely to be involved in the pathogenesis of some MCD.[2,4,13-15,20,24-28] However, to our knowledge, no study has systematically evaluated the influence of genetic or prenatal events in each of the 3 different stages of MCD.

The division of MCD into different groups is a major challenge because many important aspects, such as association with a specific genetic syndrome and pathological and neuroimaging findings, should be considered.[25,26] In our study, the diagnosis of MCD was based on well-established MRI findings, and the classification of patients into 3 groups was consistent with imaging findings. Heterotopias (subcortical or periventricular) and agyria-pachygyria (group 2) and polymicrogyria and schizencephaly (group 3) were grouped together because there is strong evidence that, in many cases, these lesions represent different ends within the spectrum of the same disease.[27]

In group 1 (focal cortical dysplasia), the frequency of family history of neurological impairment (3 patients [14%]) and the occurrence of a prenatal event (5 patients [24%]) were significantly lower compared with the other forms of MCD. In addition, none of these patients had a family history of MCD. To our knowledge, there is no description of familial cases of focal cortical dys-

**Table 3. Characteristics of Patients With Polymicrogyria or Schizencephaly (Group 3)***

| Patient No./ Age, y/Sex | Imaging Findings | Prenatal Event | Family History (No. of Relatives) | Age at First Seizure | Clinical Outcome | Cognitive Status† |
|---|---|---|---|---|---|---|
| 1/13/M | CBPS | High blood pressure | CBPS (4) | ... | ... | Normal |
| 2/3/F | Focal unilateral polymicrogyria | Fall during pregnancy | ... | ... | ... | Normal |
| 3/15/M | Schizencephaly | Abortion attempt | ... | ... | ... | Normal |
| 4/6/M | CBPS | Drug addiction | ... | ... | ... | Normal |
| 5/6/M | CBPS | Twin gestation | Developmental delay (1) | ... | ... | Normal |
| 6/9/M | CBPS | Fever; physical abuse | ... | ... | ... | Normal |
| 7/5/F | CBPS | Abortion attempt | NA | 3 y | Seizures controlled with AED | Normal |
| 8/13/M | Schizencephaly | Abortion attempt | ... | ... | ... | Normal |
| 9/17/M | Bilateral schizencephaly | Fever and skin rash | Epilepsy (2); stillbirth (1) | 4 y | Seizures controlled with AED | Mild MR |
| 10/3/M | Schizencephaly | Abortion attempt | Developmental delay (1) | 1.5 y | Seizures controlled with AED | Normal |
| 11/5/F | CBPS | Fall during 12th/16th weeks | Developmental delay (2) | 4 y | Seizures controlled with AED | Normal |
| 12/5/M | Schizencephaly | Abortion attempt; drug addiction | ... | 5 mo | Seizures controlled with AED | Normal |
| 13/11/M | CBPS | Exposure to x-rays | ... | ... | ... | Normal |
| 14/3/M | Bilateral schizencephaly | Poor prenatal care; patient put up for adoption | NA | 4 mo | Daily seizures | MR |
| 15/8/M | CBPS | Abortion attempt | ... | ... | ... | Normal |
| 16/15/M | Schizencephaly | ... | ... | 9 y | Weekly seizures | Normal |
| 17/20/M | Focal unilateral polymicrogyria | ... | ... | 3 d | Weekly seizures | Normal |
| 18/6/F | CBPS | ... | Consanguinity, epilepsy (2); CBPS (1) | ... | ... | Normal |
| 19/27/F | CBPS | ... | Epilepsy (2); CBPS (1) | ... | ... | Normal |
| 20/7/F | Schizencephaly | ... | Spontaneous abortion (1) | ... | ... | Normal |
| 21/6/M | Schizencephaly | ... | Spontaneous abortion (2) | ... | ... | Mild MR |
| 22/9/M | Schizencephaly | ... | Epilepsy (1) | 5 y | Seizures controlled with AED | Normal |
| 23/10/M | CBPS | ... | Consanguinity | 4 mo | Daily seizures | Normal |
| 24/18/F | Focal unilateral polymicrogyria | ... | ... | 12 y | Weekly seizures | Normal |
| 25/3/M | CBPS | ... | Epilepsy (2); speech delay (1) | ... | ... | Normal |
| 26/10/F | Focal unilateral polymicrogyria | ... | ... | 2 y | Seizures controlled with AED | Normal |
| 27/9/M | CBPS | ... | CBPS (4) | ... | ... Normal | |
| 28/8/F | CBPS | ... | | ... | ... | Normal |
| 29/19/M | Polymicrogyria | | Epilepsy (1) | 4 y | Monthly seizures | Normal |
| 30/2/F | Schizencephaly | ... | ... | 1 wk | Seizures controlled with AED | Normal |
| 31/25/F | Polymicrogyria | ... | MR (2) | 2 mo | Monthly seizures | Normal |
| 32/13/M | Schizencephaly | ... | MR, microcephaly (1) | ... | ... | Normal |
| 33/3/M | CBPS | ... | CBPS (4) | ... | ... | Normal |
| 34/13/M | Schizencephaly | ... | Consanguinity | 1.5 y | Seizures controlled with AED | Normal |
| 35/37/M | Schizencephaly | ... | Epilepsy (1) | 18 y | Weekly seizures | Normal |
| 36/2/F | Bilateral schizencephaly | ... | ... | ... | ... | MR |

*CBPS indicates congenital bilateral perisylvian syndrome; MR, mental retardation; AED, antiepileptic drugs; NA, not available; and ellipses, not applicable.
†Cognitive status was assessed during neurological examination.

plasia, other than those associated with specific syndromes, such as tuberous sclerosis.

In group 2, 8 patients (42%) reported a prenatal event that might have contributed to the pathogenesis of their cortical malformation, and 6 (32%) had a family history of neurological disturbances, suggesting a central nervous system lesion. However, 3 of these patients (16%) had a family history of neurological impairment and a prenatal event. Although there are several reports correlating prenatal events such as those reported by our patients and the occurrence of MCD because of abnormal migration,[18,25] it is well established that the majority of patients with the so-called migration disorders (bilateral periventricular nodular heterotopia, subcortical laminar heterotopia, agyria-pachygyria, and lissencephaly) have mutations in specific genes: *LIS-1*, *DCX*, and filamin 1.[3,7,8,10-12] We believe that MCD because of abnormal migration is mainly genetically determined, either as a familial trait or a de novo mutation; however, prenatal events could be acting in conjunction with the genetic predisposition to determine the final phenotype.

In group 3 (polymicrogyria and schizencephaly), 15 patients (42%) reported prenatal events, such as a failed abortion attempt, drug addiction, and abdominal trauma due to a fall during the first trimester of pregnancy. All of those factors could have induced a vascular injury, which

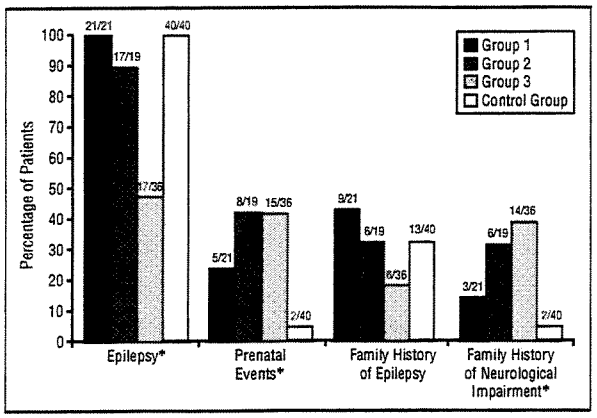


**Figure 2.** Frequency of epilepsy, prenatal events, and family history of epilepsy or neurological impairment in each group of patients with MCD and the disease-control group of patients with epilepsy. Asterisk indicates statistical significance ($P < .05$).

may play an important role as a contributor to the genesis of polymicrogyria and schizencephaly.[26] The pathologic finding of a necrotic layer in patients with layered polymicrogyria supports the traditional theory that, in many cases, these abnormalities are a form of destructive lesion.[27,29] A family history of neurological impairment, suggesting a central nervous system lesion, was also relatively common in this group (14 patients [39%]), including 5 patients (14%) who had a first-degree relative with congenital bilateral perisylvian syndrome. It is interesting to note that in this family only 1 patient had a history of prenatal injury, and he had a more severe phenotype.

Our data clearly show that prenatal events are very frequently linked to MCD. One possible limitation of this finding is the fact that information on the occurrence of prenatal events was ascertained retrospectively, and precise recollection of events that may have occurred many years before is difficult. Prenatal events, such as placental dysfunction, may be asymptomatic in the mother, which could cause a substantial underestimation of the occurrence of this kind of event. Although difficult to perform, a prospective study on the association between prenatal events and MCD would be the best way to address this issue.

We are well aware that MRI does not always detect focal cortical dysplasia and that it may be associated with other types of lesions. On the other hand, it is not known if people without epilepsy may have focal cortical dysplasia that cannot be detected with MRI. This is quite possible, judging from the fact that other types of MCD may not be associated with epilepsy. We believe that a disease-control group with epilepsy helped to differentiate factors that could be related to the seizure disorder itself and not necessarily to MCD. For example, family history of epilepsy was not significantly different among groups, but family histories of neurological impairment and prenatal events were significantly less frequent in the disease-control group. If the control group consisted of healthy subjects, there would also be a significant difference for family history of epilepsy.

Epilepsy due to MCD probably depends on many factors such as size, localization, and type of MCD lesion. The frequency of epilepsy was significantly lower and the disease was more easily controlled in group 3. These findings are in agreement with previous studies in which epilepsy was present in 57% to 87% of patients with polymicrogyria or schizencephaly.[30-34] In these studies, the epileptic spectrum was wide, and most patients had their seizures controlled with antiepileptic drugs.

In conclusion, we believe that environmental factors, such as prenatal events, may act in conjunction with genetic predisposition to determine the variable phenotypes seen in the different forms of MCD. Our findings support the idea of a clinical spectrum among the different types of MCD. Focal cortical dysplasia (group 1) is associated with more frequent and severe epilepsy and less important genetic and prenatal events, heterotopias and agyria-pachygyria (group 2) are frequently associated with genetic predisposition, and polymicrogyria and schizencephaly (group 3) are less frequently associated with epilepsy but have a stronger association with genetic and detectable prenatal events.

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**Association of Family History of Epilepsy With Earlier Age at Seizure Onset in Patients with Focal Cortical Dysplasia**

*Mayo Clinic Proceedings 2002; 77: 1291-1294.*

Original Article

# Association of Family History of Epilepsy With Earlier Age at Seizure Onset in Patients With Focal Cortical Dysplasia

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• *Objective*: To establish the contribution of family history of epilepsy to seizure onset in patients with focal cortical dysplasia (FCD).

• *Patients and Methods*: From January 1998 to January 2001, we prospectively evaluated 19 consecutive patients (10 male, 9 female) with a diagnosis of FCD based on magnetic resonance imaging. All patients and at least 1 family member were directly interviewed by the same observer after completion of a semistructured questionnaire. Initially, we classified patients into 2 groups: presence or absence of family history of epilepsy. Patients with a family history of epilepsy were subdivided into 2 groups: patients with a family history of epilepsy in first-degree relatives or multiple relatives (n=5) and patients with a family history of epilepsy in relatives who were not first-degree (n=4). Statistical analysis was performed with use of the nonparametric tests Kruskal-Wallis and Kaplan-Meier (survival analysis). $P$=.05 was considered statistically significant.

• *Results*: The ages of the patients ranged from 3 to 41 years (mean, 15.6 years). All patients had similar type and extent of cortical dysgenesis. Ages at seizure onset varied from 1 month to 22 years, with a mean of 5.8 years. Nine patients had a family history of epilepsy. The mean age at the first seizure in patients with a family history of epilepsy was 2.6 years compared with 8.5 years in those with no relatives having epilepsy ($P$=.02). When patients with a family history of epilepsy were classified further, the mean age at first seizure was 1.9 years for patients with a family history of epilepsy in first-degree or multiple relatives and 3.9 years for patients with a family history of epilepsy in relatives who were not first-degree compared with 8.5 years for patients with no family history of epilepsy ($P$=.04).

• *Conclusion*: Our results show that a family history of epilepsy is associated with an earlier age at seizure onset in patients with FCD. Although this is a preliminary finding and a larger sample is needed to confirm these results, we believe these observations provide evidence that genetic modifiers could become an important issue in the clinical presentation of patients with dysplastic lesions.

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FCD = focal cortical dysplasia; FLAIR = fluid-attenuated inversion recovery; FOV = field of view; MRI = magnetic resonance imaging; TE = echo time; TI = inversion time; TR = repetition time

Focal cortical dysplasia (FCD) was first described by Taylor et al[1] as focal disruption of the normal cortical lamination by an excess of large aberrant neurons scattered randomly through all but the first cortical layer. Since this description, FCD has been associated with refractory epilepsy, and seizure characteristics may vary according to the cortical area involved by the dysplastic lesion.[2,3]

Advances in neuroimaging, especially magnetic resonance imaging (MRI), allow noninvasive diagnosis of FCD. On MRI, FCD can be identified as an area of focal cortical thickening, blurring between the gray and white matter junction, and abnormal gyration and atrophy; sometimes it is associated with hyperintense signal on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images.[3,4] Occasionally, FCD is associated with a small trail of heterotopic neurons at the subjacent white matter connecting the cortex and the ventricular walls (Figure 1).[5]

The clinical and electroencephalographic characteristics of FCD, including its unique property of intrinsic epileptogenicity, have been reported.[2,6] However, why patients with similar lesions may experience their first seizure at extremely different ages remains unclear.

In this preliminary study, we evaluated whether genetic background influences the timing of the first seizure in patients with FCD.

## PATIENTS AND METHODS

This prospective study was conducted from January 1998 to January 2001 at the University Hospital at the University of Campinas, Campinas, Brazil. Patients were selected from adult and pediatric epilepsy clinics.

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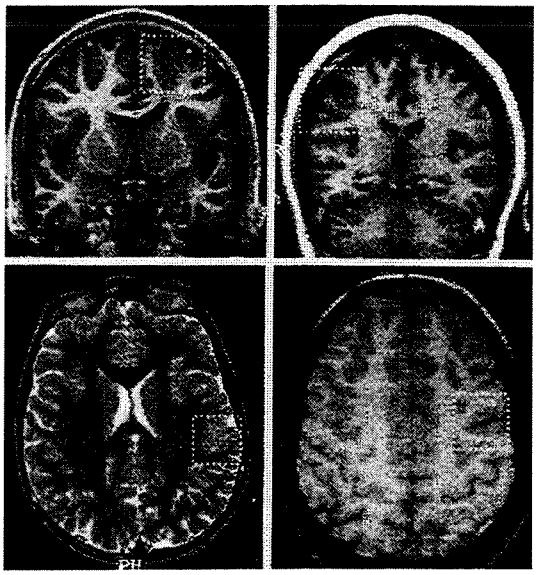

Figure 1. Clockwise from left upper corner: case 10, 17, 9, and 3. These images show focal cortical dysplasia characterized by areas of cortical thickening, abnormal gyration, and blurring between the gray and white matter (box). The image in the left upper corner (case 10) shows a trail of heterotopic neurons at the subjacent white matter connecting the cortex and the ventricular walls.

We evaluated 19 consecutive patients (10 male and 9 female) in whom FCD was diagnosed on MRI. Lesion location and size are important factors that influence the severity and age at onset of recurrent seizures. To avoid this confounding factor, we included only patients with FCD. Patients with all other types of cortical dysgenesis were excluded. The extent of FCD was restricted to 1 cerebral lobe.

All patients and at least 1 family member were directly interviewed by the same observer (M.A.M.) after completion of a semistructured questionnaire that contained specific questions about family history of epilepsy in first-, second-, and third-degree relatives. The questionnaire included (1) a family history of epilepsy; (2) relative who presented with epilepsy; (3) characteristics of the seizure, loss of consciousness, clonic movements, and need for antiepileptic drug therapy; (4) history of alcoholism, drug abuse, head trauma, brain tumor, metabolic derangements, and systemic illness or fever producing the seizures; and (5) whether the diagnosis was established by a physician.

A history of epilepsy was considered present only if the diagnosis of epilepsy had been established by a physician. Family members with seizures due to brain tumors, head trauma, and toxic or metabolic injury were excluded. Patients signed an informed consent according to the Declaration of Helsinki, and the protocol was approved by the ethics committee of our institution.

Magnetic resonance imaging was performed with a 2.0 T scanner (Elscint Prestige, Haifa, Israel) using our epilepsy protocol: (1) sagittal T1 spin-echo, 6 mm thick (repetition time [TR], 430; echo time [TE], 12) for optimal orientation of the subsequent images; (2) coronal T1 inversion recovery, 3 mm thick (flip angle, 200°; TR, 2700; TE, 14; inversion time [TI], 840; matrix, 130 × 256; field of view [FOV], 16 × 18 cm); (3) coronal T2-weighted "fast spin-echo," 3 to 4 mm thick (flip angle, 120°; TR, 4800; TE, 129; matrix, 252 × 320; FOV, 18 × 18 cm); (4) axial images parallel to the long axis of the hippocampus, T1 gradient echo, 3 mm thick (flip angle, 70°; TR, 200; TE, 5; matrix, 180 × 232; FOV, 22 × 22 cm); (5) axial T2 fast spin-echo, 4 mm thick (tip angle, 120°; TR, 6800; TE, 129; matrix, 252 × 328; FOV, 21 × 23 cm); (6) axial inversion recovery fast spin-echo FLAIR, 5 mm thick (TR, 2550; TE, 90; matrix, 250 × 250; FOV, 24 × 24 cm); (7) volumetric (3-dimensional) T1 gradient echo acquired in the sagittal plane for multiplanar reconstruction, 1 to 1.5 mm thick (tip angle, 35°; TR, 22; TE, 9; matrix, 256 × 220; FOV, 23 × 25 cm). We performed multiplanar reconstruction and curvilinear reformatting in all 3-dimensional MRIs.

The diagnosis of FCD was based on MRI findings of areas of cortical thickening, abnormal gyration, blurring between the gray and white matter junction, focal atrophy, and hyperintense signal on FLAIR or T2-weighted images.

Initially, we classified patients into 2 groups: presence or absence of family history of epilepsy. Then we subdivided the patients with a family history of epilepsy into 2 different groups: patients with a family history of epilepsy in first-degree or multiple relatives (n=5) and patients with a family history of epilepsy in relatives who were not first-degree (n=4).

Statistical analysis was performed with use of the nonparametric tests Kruskal-Wallis and Kaplan-Meier (survival analysis). $P$=.05 was considered statistically significant.

## RESULTS

The ages of the 19 patients ranged from 3 to 41 years (mean, 15.6 years). There was no significant sex difference between the 2 groups ($P$=.57, Kruskal-Wallis). The extent of FCD was restricted to 1 cerebral lobe (Figure 1) and was similar in all patients. All patients had FCD localized in the frontal lobe, except for 1 who had FCD in the occipital lobe.

All patients had partial seizures refractory to antiepileptic drugs. The 18 patients with FCD localized in the frontal regions had seizure symptoms suggestive of frontal lobe onset. The 4-year-old patient with occipital FCD did not complain of visual symptoms, and seizures were de-

scribed as generalized tonic-clonic without identifiable partial onset.

Ages at seizure onset varied from 1 month to 22 years, with a mean of 5.8 years. Nine patients had a family history of epilepsy (Table 1). The mean age at the first seizure in patients with a family history of epilepsy was 2.6 years compared with 8.5 years in those with no relatives having epilepsy ($P$=.02, Kruskal-Wallis). Kaplan-Meier survival analysis confirmed the difference between these 2 groups ($P$=.02; Figure 2).

When patients with a family history of epilepsy were classified further, the mean age at the first seizure was 1.9 years for patients with a family history of epilepsy in first-degree or multiple relatives and 3.9 years for patients with a family history of epilepsy in relatives who were not first-degree compared with 8.5 years for patients with no family history of epilepsy. Kaplan-Meier survival analysis showed significant differences among groups ($P$=.04).

Magnetic resonance imaging was performed in only 1 family member who had epilepsy, and it showed no abnormalities.

Table 1. **Clinical Characteristics of 19 Patients With Focal Cortical Dysplasia**

| Patient/ age (y)/sex | Family history (No. of affected relatives) | Age at first seizure |
|---|---|---|
| 1/3/F | Epilepsy (1 third-degree) | 1 mo |
| 2/6/M | Epilepsy (3 second-degree) | 4 mo |
| 3/7/M | Epilepsy (1 second-degree) | 1.5 y |
| 4/19/F | Epilepsy (1 first-degree) | 6 y |
| 5/4/F | Epilepsy (2 second-degree) | 9 mo |
| 6/25/F | Epilepsy (1 second-degree) | 2 y |
| 7/20/M | Epilepsy (1 second-degree) | 12 y |
| 8/4/M | Epilepsy (2 second-degree, 2 third-degree) | 2 y |
| 9/10/M | Epilepsy (1 second-degree and 3 third-degree) | 7 mo |
| 10/13/M | None | 6 y |
| 11/29/F | None | 14 y |
| 12/16/M | None | 9 y |
| 13/7/M | None | 2 y |
| 14/24/F | None | 10 y |
| 15/19/M | None | 16 y |
| 16/4/F | None | 2 y |
| 17/41/F | None | 1.5 y |
| 18/38/M | None | 22 y |
| 19/9/F | None | 3 y |

## DISCUSSION

The underlying mechanism leading to FCD has not yet been established; however, it is likely that all 3 fundamental stages of cortical development (proliferation-apoptosis, migration, and organization) are involved in FCD genesis.[4]

Patients with FCD are usually intellectually normal, neurologic examination reveals no focal deficits, and epilepsy may be the only clinical manifestation. However, when seizures are refractory to antiepileptic drugs, surgical resection of the dysplastic lesion is often the treatment of choice.[2] Epilepsy due to FCD may begin in patients at different ages, and the timing of the first seizure probably depends on many factors, such as the size, localization, and pathological characteristics of the lesion.

In the current study, all patients had similar type and extent of cortical dysgenesis. We found that the subgroup of patients with a family history of epilepsy had a significantly earlier age at seizure onset compared with those with no family history of epilepsy. In addition, the classification of the subgroup of patients with FCD and family history of epilepsy into those with a family history of epilepsy in first-degree or multiple relatives vs those with a family history of epilepsy in second- or third-degree relatives continued to show differences in mean age at seizure onset.

Genetic predisposition may play an important role in controlling seizure onset in patients with idiopathic and cryptogenic epilepsies.[7] Moreover, in animal models of cortical dysplasia, only those produced by genetic alterations have documented spontaneous seizures.[8] Our findings suggest that in patients with genetic predisposition to epilepsy, determined by the presence of a family history of epilepsy, seizure onset may be anticipated in the setting of FCD.

We acknowledge that pathological verification in all 19 patients would have better validated our findings. However, we also believe that the neuroimaging characteristics of FCD are well established and that FCD can be diag-

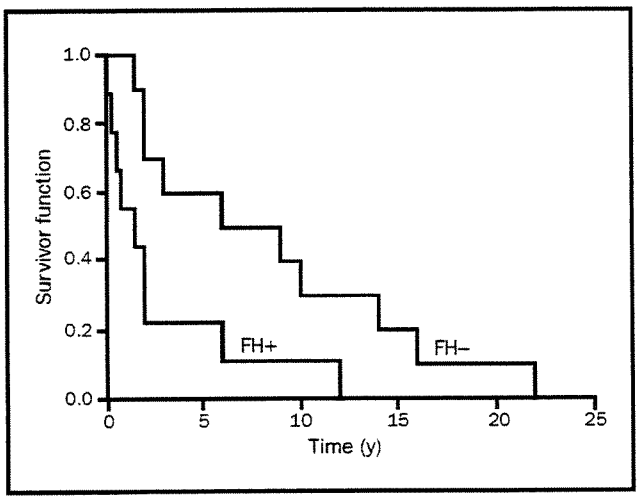


Figure 2. Survival plot (Kaplan-Meier) analysis of the age of patient at first seizure in patients with (FH+) vs those without (FH–) a family history of epilepsy ($P$=.02).

nosed with confidence based only on imaging findings when clinical and electroencephalographic data indicate that the epileptogenic region is colocalized with the lesion.[9]

Magnetic resonance imaging was performed in only 1 family member with epilepsy and showed no abnormalities. Identifying FCD in family members without epilepsy would be difficult because lesions are usually subtle, and clinical correlation is a valuable aid in diagnosing FCD. To our knowledge, no familial cases of FCD have been described, except when associated with specific syndromes, such as tuberous sclerosis.

Another issue that should be considered is the fact that prior experience with epileptic seizures may lead to earlier recognition of more subtle or partial seizures in probands with a family history of epilepsy. However, in our study, careful interviews with the mothers and patients allowed retrospective determination of the timing of the first seizure, even in families without a history of epilepsy.

## SUMMARY

Our study showed that a family history of epilepsy is associated with an earlier age at seizure onset in patients with FCD, thus suggesting that the clinical presentation in these patients is influenced by genetic predisposition. Although this is a preliminary finding and a larger sample must be assessed to confirm these results, we believe that these observations provide evidence that genetic modifiers could become an important issue in determining the clinical presentation of patients with dysplastic lesions.

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# Capítulo III

# Espectro clínico e eletrencefalográfico das malformações do desenvolvimento cortical

Artigo 4 - Bilateral posterior parietal polymicrogyria: a mild form of congenital bilateral perisylvian syndrome?

Artigo 5 - Developmental language disorder associated with polymicrogyria

Artigo 6 - Variable presentation and severity of epilepsy in the different types of malformations of cortical development

**Bilateral Posterior Parietal Polymicrogyria: A Mild Form of Congenital Bilateral Perisylvian Syndrome?**

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Blackwell Science, Inc.


# Bilateral Posterior Parietal Polymicrogyria: A Mild Form of Congenital Bilateral Perisylvian Syndrome?

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**Summary:** *Purpose:* The main features of congenital bilateral perisylvian syndrome (CBPS) are pseudobulbar palsy, cognitive deficits, epilepsy, and perisylvian abnormalities on imaging studies, however, the clinical spectrum of this syndrome is much wider than previously believed and may vary from minor speech difficulties to severely disabled patients. The objective of this study was to present the different imaging and clinical findings of 17 patients with CBPS, their genetic background, and the occurrence of prenatal injury during their pregnancies.

*Methods:* We evaluated 17 consecutive patients with CBPS and divided them into two groups according to the imaging findings: (a) diffuse polymicrogyria around the sylvian fissure and (b) posterior polymicrogyria at the posterior parietal regions. They were systematically interviewed regarding history of prenatal events during their pregnancies, family history of speech difficulties, epilepsy, or other neurologic abnormality.

*Results:* There were seven women, ages ranging from 3 to 41 years (mean, 11.5; median, 7 years). Seven patients had bilateral posterior parietal polymicrogyria (BPPP), and 10 had diffuse bilateral perisylvian polymicrogyria. All seven patients with BPPP had only minor speech difficulties, none had epilepsy, and all but one had a family history of epilepsy or cortical dysgenesis. In contrast, 10 patients with diffuse bilateral perisylvian polymicrogyria had pseudobulbar palsy, four had epilepsy, eight had a history of a major prenatal event, and only four had a family history of epilepsy or developmental delay.

*Conclusions:* These findings suggest that diffuse bilateral perisylvian polymicrogyria appears to be more related to injuries caused by environmental factors, whereas BPPP has a stronger genetic predisposition. In addition, BPPP appears to have a wider clinical spectrum than previously believed, and may represent a milder extreme within the spectrum of CBPS.

**Key Words:** Perisylvian polymicrogyria—Cortical dysgenesis—Prenatal events.

The main features of congenital bilateral perisylvian syndrome (CBPS) are pseudobulbar palsy, cognitive deficits, epilepsy, and perisylvian abnormalities on imaging studies (1,2). The cortical abnormality seen in the perisylvian region is consistent with polymicrogyria and is usually symmetric but varies in extent among patients (2,3). Guerrini et al. (4) reported that sometimes the polymicrogyria may involve only the anterior portion of the sylvian fissure; it can be restricted to the posterior regions (parietooccipital cortex) or both, extending posteriorly from the sylvian fissure across the entire hemispheric convexity. They suggest a malformative pattern bordering a line passing through the sylvian fissure and directed posteriorly and upward to the mesial aspect of the hemispheric convexity (4).

Guerreiro et al. (1) recently described the familial occurrence of CBPS in 12 pedigrees, showing that the neuroimaging and clinical spectrum of this syndrome is much wider than previously believed. The systematic investigation of family members of patients with the classic clinical presentation of CBPS led to the identification of almost asymptomatic individuals with neuroimaging investigation showing bilateral posterior parietal polymicrogyria (BPPP), most of them only with a previous history of speech delay or mild dysarthria.

The objective of this study was to present the different imaging and clinical findings of 17 patients with CBPS seen at our university hospital, their genetic background, and the association with prenatal events that occurred in the first two trimesters of their pregnancies.

## METHODS

We evaluated all patients with the diagnosis of perisylvian polymicrogyria, confirmed by magnetic resonance imaging (MRI) (n = 16) or computed tomography (CT) scan (n = 1), seen consecutively at our university hospital from January 1998 to June 2000. MRI was performed in a 2.0-T scanner (Elscint Prestige, Haifa, Israel), using our epilepsy protocol: (a) sagittal $T_1$ spin-echo, 6-mm thick (TR = 430, TE = 12) for optimal

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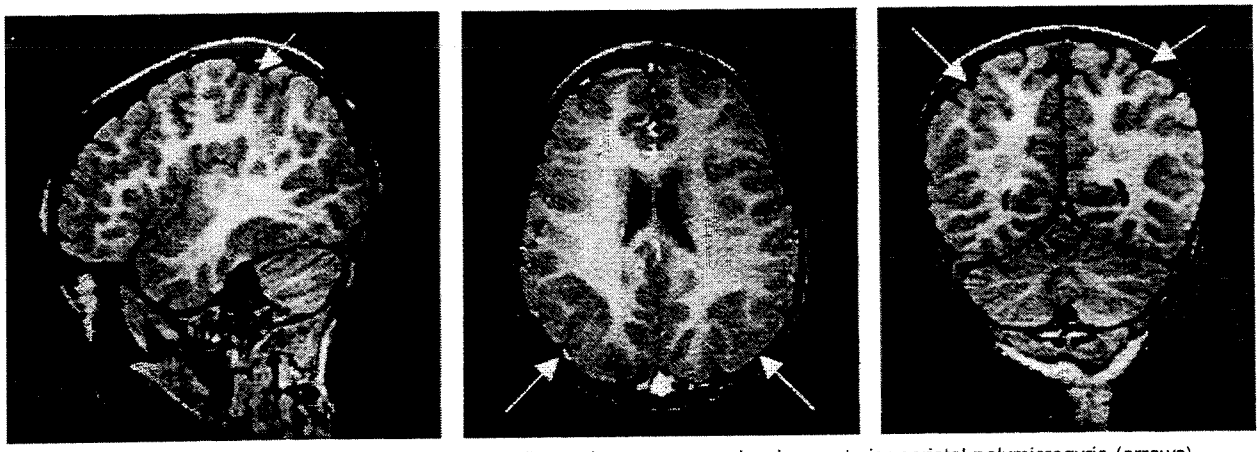

**FIG. 1.** Patient 5: Sagittal, axial, and coronal gradient-echo sequences showing posterior parietal polymicrogyria (arrows).

orientation of the subsequent images; (b) coronal $T_1$ inversion recovery, 3-mm thick (flip angle = 200 degrees; TR = 2,800–3,000, TE = 14, inversion time $T_1$ = 840, matrix = 130 × 256, FOV = 16 × 18 cm); (c) coronal $T_2$-weighted "fast spin echo" (FSE), 3- to 4-mm thick, (flip angle = 120 degrees; TR = 4,800, TE = 129, matrix = 252 × 320, FOV = 18 × 18 cm), (d) axial images parallel to the long axis of the hippocampi; $T_1$ gradient echo (GRE), 3 mm thick (flip angle = 70 degrees, TR = 200, TE = 5, matrix = 180 × 232, FOV = 22 × 22 cm); (e) axial $T_2$ FSE, 4 mm thick, (tip angle 120 degrees, TR = 6,800, TE = 129, matrix 252 × 328, FOV = 21 × 23 cm); (f) Volumetric (3D) $T_1$ GRE, acquired in the sagittal plane for multiplanar reconstruction (MPR), 1–1.5 mm thick (TA = 35 degrees, TR = 22, TE = 9, matrix = 256 × 220, FOV = 23 × 25 cm). We performed MPR and curvilinear reformatting in all 3D MRIs (5).

Patients and families were interviewed and specifically questioned about family history of epilepsy or any neurologic abnormality and the occurrence of prenatal events during the first two trimesters of their pregnancies. All patients were seen and examined by at least one of us.

We systematically investigated family members of patients with the classic clinical presentation of CBPS and any patient with language disturbances. MRI was performed in five additional family members because of the presence of language disturbances or family history of speech delay, and four of them showed cortical abnormalities consistent with BPPP. These four patients were included in this study (patients 1, 2, 3, and 6).

Patients were divided into two groups according to neuroimaging findings: (a) diffuse polymicrogyria around the entire extent of the sylvian fissure, including its extension posteriorly to the parietooccipital regions, and (b) polymicrogyria restricted to the posterior aspects of the parietooccipital regions (BPPP), without any cortical abnormality at the anterior two thirds of the sylvian fissure.

## RESULTS

Seventeen patients with the diagnosis of CBPS were included, seven women (Table 1). Ages ranged from 3 to

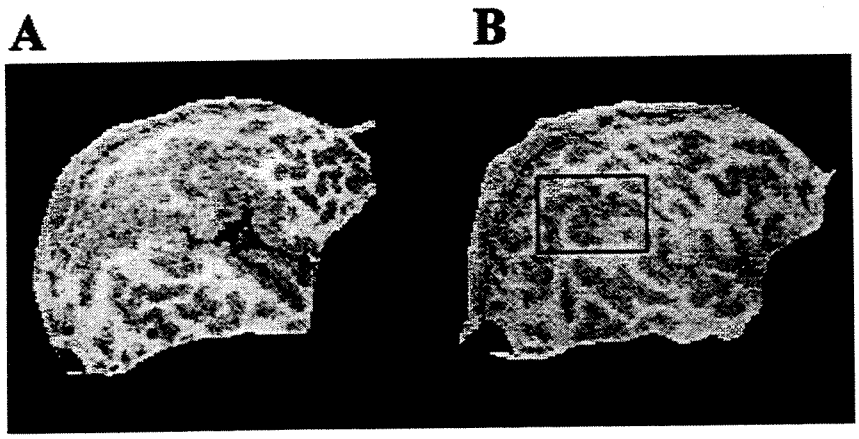


**FIG. 2.** Curvilinear reconstruction at 12 mm of depth from the cortical surface showing **(A)** patient 10: diffuse perisylvian polymicrogyria; and **(B)** patient 5: posterior parietal polymicrogyria (box).

**TABLE 1.** *Characteristics of the 17 patients with congenital bilateral perisylvian syndrome*

| Patient | Age (yr/gender) | Family history | Prenatal events | Epilepsy | Age at first seizure | Seizure frequency | Neurologic findings | Localization of MRI abnormalities |
|---|---|---|---|---|---|---|---|---|
| 1[a] | 10/M | CBPS | ---- | ---- | ---- | ---- | Mild dysarthria | Posterior parietal |
| 2[a] | 3/M | CBPS | ---- | ---- | ---- | ---- | Speech delay | Posterior parietal |
| 3[a] | 32/F | CBPS | ---- | ---- | ---- | ---- | Mild dysarthria | Posterior parietal |
| 4[b] | 6/F | Epilepsy, speech delay, CBPS | Consanguinity | ---- | ---- | ---- | Speech delay | Posterior parietal |
| 5 | 3/M | Epilepsy, speech delay | ---- | ---- | ---- | ---- | Speech delay | Posterior parietal |
| 6[b] | 27/F | Epilepsy, speech delay, CBPS | ---- | ---- | ---- | ---- | Asymptomatic | Posterior parietal |
| 7 | 8/M | ---- | Abortion attempt | ---- | ---- | ---- | Speech delay, PBP | Diffuse |
| 8 | 5/F | NA | Abortion attempt, adopted | Partial seizures | 3 yr | Controlled with AED | Tetraparesis, PBP | Diffuse |
| 9 | 5/F | Developmental delay | Fall between 12 and 16 gestational wk | Partial seizures | 4 yr | Controlled with AED | Mild left hemiparesis | Diffuse |
| 10 | 9/M | ---- | Consanguinity | Lennox–Gastaut syndrome | 4 mo | Daily seizures | Tetraparesis, PBP | Diffuse |
| 11 | 41/F | Epilepsy and developmental delay | ---- | Partial seizures | 14 yr | One seizure/mo | Tetraparesis, worse on the right side and PBP | Diffuse |
| 12[a] | 13/M | CBPS | High blood pressure | ---- | ---- | ---- | PBP | Diffuse |
| 13 | 6/M | ---- | Drug addiction | ---- | ---- | ---- | PBP and mild right hemiparesis | Diffuse |
| 14 | 11/M | ---- | Exposure to x-ray | ---- | ---- | ---- | PBP | Diffuse |
| 15 | 5/F | | Fever at gestational wk 24 | ---- | ---- | ---- | Dysarthria and PBP | Diffuse |
| 16 | 7/M | ---- | ---- | ---- | ---- | ---- | Speech apraxia | Posterior parietal |
| 17 | 6/M | Developmental delay | Twin pregnancy | ---- | ---- | ---- | Speech delay and mild PBP | Diffuse |

[a,b]Patients belong to the same family.
NA, not available; AED, antiepileptic drug; CBPS, congenital bilateral perisylvian syndrome; PBP, pseudobulbar palsy.

41 years (mean, 11.5; median, 7 years). Ten patients had a family history of neurologic abnormalities, including CBPS, epilepsy, or speech or developmental delay. Two patients had consanguineous parents. In eight patients, a history of a major prenatal event was reported: abortion attempt in two patients, a fall between gestational weeks 12 and 16, exposure to x-rays, drug addiction, twin pregnancy, and fever or maternal high blood pressure during pregnancy requiring hospitalization in one patient each.

MRI (n = 16) or CT scan (n = 1) showed BPPP in seven and diffuse perisylvian polymicrogyria in 10 patients. All patients had bilateral perisylvian abnormalities, which were asymmetric in three (patients 9, 11, and 13). Patients with imaging abnormalities restricted to the posterior parietal region had normal neurologic examinations except for speech delay in early infancy (patients 2, 4, 5, and 16) or mild dysarthria later in life (patients 1 and 3). Patients with more diffuse polymicrogyria, throughout most of the perisylvian fissure, had more severe symptoms, characterized by pseudobulbar palsy (patient 7, 12, 14, 15, and 17) and/or motor involvement (patients 8, 9, 10, 11, and 13). Eight of the 10 patients with diffuse polymicrogyria (7, 8, 9, 12, 13, 14, 15, and 17) had a history of a major prenatal injury.

Four patients with diffuse bilateral perisylvian polymicrogyria had epilepsy. Patient 10 reported daily seizures, and EEGs showed features of Lennox–Gastaut syndrome; the other three patients had partial seizures, which were easily controlled with antiepileptic drugs (AEDs) in two (patients 8 and 9). None of the patients with BPPP had epilepsy.

## DISCUSSION

Polymicrogyria is an anomaly of cortical development in which neurons reach the cortex but are abnormally distributed, resulting in the formation of multiple small gyri (6). Two patterns of polymicrogyria are recognized, layered and unlayered. In layered polymicrogyria, instead of the six layers usually present in the normal cortex, only four are seen: molecular, outer cellular, cell sparse (necrotic), and inner cellular (7). These findings support the traditional theory that in many cases, these abnormalities represent a form of destructive lesion, probably due to an early vascular injury (7,8). Barkovich and Kjos (8) suggested that a superficial cortical injury will result in flat polymicrogyria without cortical infolding; a more severe injure, that extends deeply into the hemisphere and destroy completely the radial glial fibers, results in schizencephaly, and a partial destruction of the radial glial fibers will result in cortical infolding. Guerrini et al. (9) described nine patients with parietooccipital polymicrogyria associated with epilepsy and cognitive slowing, and proposed that its location in a watershed area between anterior and posterior cerebral arteries suggests a postmigration perfusion failure as the underlying cause. However, they did not report any family history of neurologic abnormalities or etiologic factors.

Since the description of familial cases of CBPS in 12 pedigrees, the neuroimaging and clinical spectrum of this syndrome was proven to be much wider than previously believed (1). However, patients with polymicrogyria restricted to the posterior portion of the sylvian fissure at the parietooccipital regions are difficult to diagnose because the lack of neurologic signs, relatively late seizure onset, difficulty in localizing seizure onset, and inability to recognize the cortical abnormality on CT scans (9). Our systematic investigation of family members of patients with the classic clinical presentation of CBPS led to the identification of almost asymptomatic individuals with neuroimaging findings showing BPPP, most of them only with a history of speech delay in early childhood or mild dysarthria.

Our patients with CBPS had a very interesting distribution: patients with a milder form (BPPP) had a strong family history of CBPS or speech delay, and patients with the diffuse form reported major early prenatal events, such as an abortion attempt that may have induced a vascular injury during cortical development. Because the fetal sulci appear in an orderly sequence, and the primitive sylvian fissure (the earliest fetal sulcus) appears during the fifth gestational month and is followed by the rolandic (central), interparietal, and superior temporal sulci, which appear toward the end of the sixth and beginning of the seventh gestational months (10), we believe that a perfusional failure involving the middle cerebral artery circulation in early stages of cerebral sulci development produces the diffuse form of CBPS. By contrast, a less severe or later event that may compromise only the watershed areas might produce the milder (posterior parietoocipital) form of CBPS, as suggested by Guerrini et al. (9).

Patients with lesions of the supplementary motor or posterior parietal association cortices have apraxia, which is characterized by inability to perform complex acts requiring sequences of muscle contractions or a planned strategy, despite the absence of weakness or sensory loss (11). Clinically, our patients with BPPP did not have pseudobulbar palsy or other motor deficits, but only speech delay or minor speech difficulties, particularly during stress, which may represent speech dyspraxia. This is in keeping with their imaging findings, in which the cortical abnormality spares the motor cortex and opercular regions. It is important to emphasize that all seven patients with BPPP do not have epilepsy and were identified due to the systematic neuroimaging investigation of patients with language disturbances.

Epilepsy associated with CBPS has a wide spectrum. Seizures may be easily controlled with AEDs, but some patients may have severe epileptic encephalopathies such as West syndrome (1). We believe that because most of the reports about localized polymicrogyria come from surgical series, the frequency of patients with epilepsy is probably overestimated. Patients with only mild speech delay or dysarthria usually are not investigated with high-resolution MRI unless they have epilepsy.

The description of familial cases of polymicrogyria, particularly CBPS, brings a new perspective to its etiology (1). In this study, patients 1, 2, 3, and 12 are part of the same family that exhibits a wide clinical presentation: three patients nearly asymptomatic, without abnormal tongue movements (patients 1, 2, and 3), and one (patient 12) with pseudobulbar palsy and history of a prenatal event (maternal high blood pressure). Patient 12 was the only one in this family with the diffuse perisylvian form, demonstrating that a major prenatal event in an already genetically predisposed individual may result in a more diffuse lesion and, consequently, a more severe phenotype. These findings are also in agreement with the study of Barkovich et al. (12), which suggests that when the area of polymicrogyria is extensive, it appears to be the addition of more than one affected cortical region. A fifth family member with mental retardation and epilepsy was not included in this study because imaging studies were unavailable [this family has already been described in detail elsewhere] (1).

Our findings suggest that BPPP has a broader spectrum than previously believed and may be a milder extreme within the spectrum of CBPS. BPPP appears to be associated with a genetic predisposition, whereas the diffuse and more severe form appears to occur more often in individuals with major prenatal events. These environmental factors may act in conjunction with genetic predisposition to determinate the different phenotypes seen in familial forms of polymicrogyria.

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**Developmental language disorder associated with polymicrogyria**

*Neurology 2002; 59: 245-250.*

CME

# Developmental language disorder associated with polymicrogyria

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**Abstract**—*Background:* Subtle disorders of neuronal migration occur in the brains of some dyslexic patients who presented developmental language disorder (DLD) during early childhood. *Objective:* To investigate a possible neuroanatomical substrate based on neuroimaging evaluation in children with DLD. *Methods:* The authors obtained psychological assessment, language evaluation, neurologic examination, and neuroimaging investigation. Inclusion criteria were as follows: children should be at least 4 years of age; primary complaint of language delay; normal hearing; IQ >70; and an informed consent form signed by parents or guardians. Exclusion criteria were severe motor and cognitive handicap. *Results:* Fifteen children met all inclusion criteria. Ages ranged from 4 to 14 years and 11 were boys. Six patients presented diffuse polymicrogyria (PMG) around the entire extent of the sylvian fissure on MRI, and they had severe clinical manifestation of DLD: they did not speak at all or had mixed phonologic–syntactic deficit syndrome. Six children presented PMG restricted to the posterior aspects of the parietal regions, and they had a milder form of DLD: mainly phonologic programming deficit syndrome. The other three children had different imaging findings. *Conclusions:* Developmental language disorder can be associated with polymicrogyria and the clinical manifestation varies according to the extension of cortical abnormality. A subtle form of posterior parietal polymicrogyria presenting as developmental language disorder is a mild form of perisylvian syndrome.

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Developmental language disorder (DLD), also known as developmental language impairment or developmental dysphasia, refers to inadequate language acquisition at the expected age in children with otherwise ostensibly normal development.[1] DLD encompasses deficits in comprehension, production, and use of language that is not in keeping with a child's mental age. Nonverbal cognitive skills are usually normal or near normal. Children with mental deficiency and autism have problems with communication, but language deficit is part of a much broader scenario. Therefore, DLD is applied when specific conditions involving exclusively or mainly the language domain are considered.

Subtle disorders of neuronal migration were found in the brains of some dyslexic patients who presented DLD during early childhood.[2,3] Despite these results, there is no consistent structural abnormality underlying DLD.[4,5] It is also a current belief that imaging techniques have no place in the routine investigation of dysphasic children.[1]

We investigated a group of children with DLD to determine if there are neuroimaging abnormalities.

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

**Patients and methods.** We prospectively studied every child presenting with language delay seen at our Child Neurology Outpatient Clinic between January 1998 and January 2000. Our examination included the following: psychological assessment, language evaluation, neurologic examination, and neuroimaging investigation. Inclusion criteria were as follows: children should be at least 4 years of age; primary complaint of language delay; normal hearing by audiometry; IQ >70; and an informed consent form signed by parents or guardians giving permission for their children to take part in this research. Exclusion criteria were severe motor or cognitive handicap. The protocol and the informed consent were approved by the ethical committee of our university hospital.

*Psychological assessment.* Intellectual ability was assessed by the Wechsler Intelligence Scale for Children–III (WISC-III) or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). Because language delay was a requirement to enter the study, our patients usually had verbal IQ much lower than performance IQ. Full-scale was jeopardized by low verbal scores. We decided to take into account only the performance IQ because it better represents the cognitive ability of this type of patient.

*Language evaluation.* We used the Peabody Picture Vocabulary Test–revised (PPVT), Brazilian standardization by Capovilla and Capovilla,[6] to evaluate auditory–receptive vocabulary.

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Nonstandardized protocol. Spontaneous language was recorded on VHS video during a 1-hour play session. We systematically evaluated, according to a semistructured protocol, free conversation, repetition, and the following aspects of language: phonologic, syntactic, semantic, pragmatic, and lexical.

*Phonologic production:* Type of phonologic alterations included delayed (phonologic simplifications no longer expected at the chronologic age; however, observed in the normal language); deviant (phonologic simplifications not found in the normal language development); and inaccurate (wide variation in the articulation of words and increase in the amount of syllable reductions as word extension increases).

*Morphosyntactic production (syntax):* Sentence structure; nominal and verbal concordance.

*Semantic–lexical production:* Predominant form of access to lexicon: access using the appropriate lexicon (even with a few words); access using idiosyncrasies; access using periphrases (the use of two or more words instead of an inflected word to express the same grammatic function, e.g., "that's to eat" instead of "spoon"); and deictics.

*Pragmatic evaluation:* Conversational abilities (ample, restricted) and communicative functions (ample, restricted).

*Comprehension evaluation:* Understanding of at least 10 short enunciations (example: "get the pencil"), and 10 long enunciations (example: "get the pencil and put it on the table") with words that have lexical and grammatic meaning.

For children that did not speak or who spoke with restrictions (scattered words and phrases) the language evaluation used the following analysis criteria: intentionality, functionality, engaging in dialogue activities, means of communication, and level of comprehension.

Language evaluation was performed by a child speech therapist (S.R.V.H.) who specialized in language development. The aim was to categorize abnormal language findings according to the classification proposed by Allen et al.[7]:

*Excessive use of jargons:* Children are fluent but lack intelligibility; comprehension is adequate; sentence structure is generally good, but grammatical markers may be omitted. This has been referred to as a "phonologic programming deficit" by Allen et al.[7]

*Verbal dyspraxia:* Children are severely dysfluent, with very impaired speech articulation but good comprehension.

*Phonologic–syntactic deficit:* Children are dysfluent and speak in simplified sentences; they may omit syntactic markers; speech articulation is deficient; comprehension is variable.

*Verbal auditory agnosia:* Children understand little or nothing of what they hear because they are unable to decode language at the level phonology; speech is absent or very limited.

*Lexical–syntactic deficit:* children have word-finding problems and difficulty in formulating connected language; syntax is immature rather than deviant; phonology is intact; comprehension of complex sentences is poor.

*Semantic–pragmatic deficit:* Children are fluent and often verbose, but the content of language is bizarre and they may be echolalic or use overlearned scripts; adequate articulation.

Some children could not be adequately classified because the limited utterance did not allow a precise differentiation among the multiple subtypes of DLD. Because they showed impairment of both comprehension and expression, we classified them under "global disorder."

*Neurologic examination.* A detailed neurologic examination was performed and signs of pseudobulbar palsy were specifically investigated. Tongue movements (protrusion, lateral, and upward movements) were examined, and the presence of dysarthric speech, abnormal gag reflex, brisk jaw jerk and automatic–voluntary dissociation of facial movements was specifically noted.

Children with mild motor development delay (gait acquisition between 18 and 24 months of age) were included in the study as long as language developmental delay was the primary complaint.

Parents or guardians were specifically questioned about a history of drooling, choking, feeding difficulties in the neonatal period, swallowing and sucking problems, and current difficulty in whistling or blowing. The family history was carefully searched.

*MRI.* Neuroimaging investigation was performed in a 2.0 T scanner (Elscint Prestige) using the following protocol: 1) sagittal T1-weighted spin-echo, 6-mm-thick (repetition time [TR] = 430, echo time [TE] = 12), for optimal orientation of the subsequent images; 2) coronal T1-weighted inversion recovery, 3-mm-thick (flip angle = 200°; TR = 2,800 to 3,000, TE = 14, inversion time [TI] = 840, matrix = 130 × 256, field of view [FOV] = 16 × 18 cm); 3) coronal T2-weighted fast spin-echo (FSE), 3- to 4-mm-thick (flip angle = 120°; TR = 4,800, TE = 129, matrix = 252 × 320, FOV = 18 × 18 cm); 4) axial images parallel to the long axis of the hippocampi; T1 gradient echo (GRE), 3-mm-thick (flip angle = 70°, TR = 200, TE = 5, matrix = 180 × 232, FOV = 22 × 22 cm); 5) axial T2 FSE, 4-mm-thick (flip angle = 120°, TR = 6,800, TE = 129, matrix = 252 × 328, FOV = 21 × 23 cm); 6) volumetric (three-dimensional) T1 GRE, acquired in the sagittal plane for multiplanar reconstruction (MPR), 1-mm-thick (flip angle = 35°, TR = 22, TE = 9, matrix = 256 × 220, FOV = 23 × 25 cm). We performed MPR and curvilinear reformatting in all three-dimensional MRI scans.[8]

**Results.** From January 1998 to January 2001, 29 consecutive children with primary complaint of language delay were evaluated. Fourteen were excluded because of a global developmental delay, psychological evaluation revealed IQ <70, or because they did not complete all steps of the protocol. The remaining 15 children met all inclusion criteria and are the subjects of this study.

Ages ranged from 4 to 14 years (mean = 6.8) and 11 were boys. Demographic data, psychological evaluation (IQ and handedness), history of pseudobulbar difficulties, family history of developmental language delay, motor development, results of neurologic examination including the careful search for pseudobulbar signs, and neuroimaging findings are presented in table 1. Regarding imaging ab-

*Table 1 Summary data of 15 patients with developmental language disorder (DLD)*

| Patient no./ age, y/sex | Performance IQ/verbal IQ | Handedness | History of pseudobulbar difficulties | Family history of DLD | Motor development | | Neurologic examination* | Pseudobulbar signs | MRI† |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Normal | Mild delay | | | |
| 1/4/M | 80/NA | R | – | + | + | – | Normal | – | Bilateral Posterior Parietal PMG |
| 2/4/M | 100/100 | R | – | + | + | – | Normal | – | Bilateral Posterior Parietal PMG |
| 3/6/M | 107/79 | R | – | + | – | + | Normal | – | Bilateral Posterior Parietal PMG |
| 4/6/M | 126/110 | R | – | + | + | – | Normal | – | Bilateral Posterior Parietal PMG |
| 5/7/M | 88/56 | R | – | + | – | + | Normal | – | Bilateral Posterior Parietal PMG |
| 6/7/M | 88/66 | R | + | – | – | + | Normal | + | Bilateral Posterior Parietal PMG |
| 7/4/F | 90/NA | R | + | + | – | + | Normal | + | Diffuse Bilateral PS PMG |
| 8/4/F | 77/60 | R | + | + | + | – | Normal | + | Diffuse Bilateral PS PMG |
| 9/8/M | 100/79 | R | + | – | + | – | Normal | + | Diffuse Bilateral PS PMG |
| 10/9/M | 75/46 | L | + | – | – | + | Normal | + | Diffuse Bilateral PS PMG |
| 11/14/M | 83/11 | R | + | + | + | – | Normal | + | Diffuse Bilateral PS PMG |
| 12/5/M | 88/NA | L | + | – | – | + | Mild R hemiparesis | + | Diffuse Bilateral PS PMG |
| 13/8/F | 79/50 | R | + | – | – | + | Normal | + | R Frontal PMG |
| 14/12/M | 83/50 | L | – | + | – | + | Normal | – | Hypogenesis of CC + Chiari I |
| 15/4/F | 80/NA | R | – | – | + | – | Normal | – | Bilateral Frontal Parietal atrophy |

* Refers to strength, deep tendon reflexes, sensory system, cranial nerves, and coordination.

† Representative samples of MRI for Patients 1 through 10 can be accessed on the supplementary data on the *Neurology* Web site. Figures 1 and 2 illustrate MRI findings of Patients 11 and 12.

NA = not applicable; – = absent; + = present; PMG = polymicrogyria; PS = perisylvian; CC = corpus callosum.

normalities, the term diffuse polymicrogyria (PMG) was used when the cortical abnormality occurred around the entire extent of the sylvian fissure, including the parietal region (figure 1), whereas the term posterior parietal PMG was used when PMG was restricted to the posterior aspects of the parietal regions, without MRI abnormality at the anterior two-thirds of the sylvian fissure. Only two children (Patients 6 and 9) showed asymmetry of polymicrogyric cortex, which predominated on the left. All other children with PMG presented symmetrical bilateral PMG (figure 2). Additional figures with representative samples of imaging abnormalities can be found in the supplementary information on the *Neurology* Web site (go to www.neurology.org and scroll down the Table of Contents to find the title link for this article).

Table 2 shows the results of the language assessment.

The analysis of the results presented in both tables prompted a further division of the findings according to the extent of the polymicrogyric cortex and the severity of the clinical manifestation: patients with posterior parietal cortical involvement tended to present with a milder form of DLD (Patients 1 through 6), while diffuse polymicrogyric perisylvian cortex involving precentral and frontal regions usually was seen in patients who presented with a severe clinical manifestation (Patients 7 through 12). The other three children had different imaging findings: one child had right frontal PMG on MRI (Patient 13), one had hypogenesis of the corpus callosum and Chiari I (Patient 14), and one had bilateral frontoparietal atrophy (Patient 15).

**Discussion.** Studies have shown nonspecific MRI findings[4,5] in patients with developmental language disorder (DLD); however, there have been no definite structural brain abnormalities associated with DLD.[1] In the current study, we described clear-cut MRI abnormalities in cortical areas involved in language processing in a group of 15 consecutive patients with DLD. All but three patients had PMG in variable degrees involving perisylvian regions or

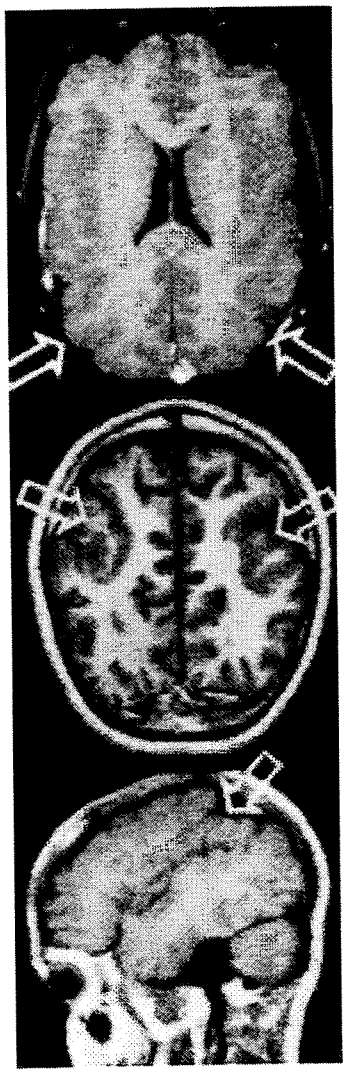

*Figure 1. (Patient 11). Axial, coronal and sagittal T1-weighted images showing polymicrogyria around the sylvian fissure.*

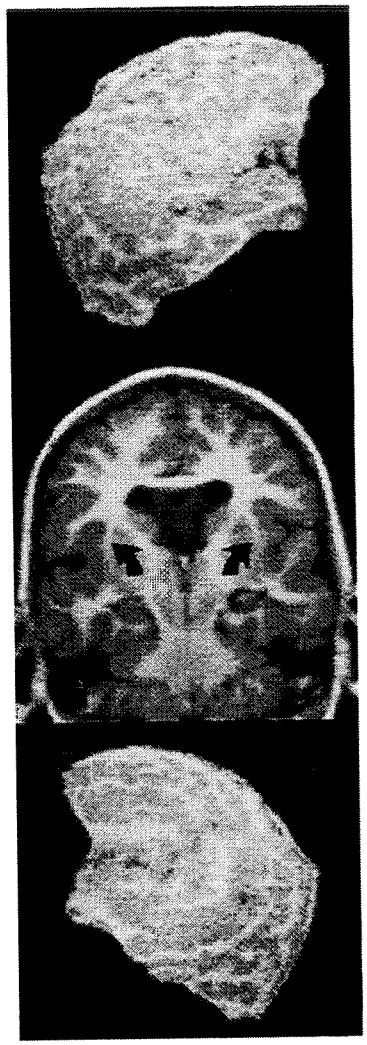

*Figure 2. (Patient 12). Curvilinear reformatting from 12 mm of depth from the cortical surface and coronal T1/IR image (thickness = 3 mm) showing diffuse polymicrogyria around the perisylvian fissure. Note that thin slices and image postprocessing techniques improve the visual display of subtle lesions on MRI.*

temporoparietal areas. The MRI diagnosis was based on detailed visual analysis of thin slices (3 mm or less) of high-resolution MRI, including techniques of image postprocessing such as multiplanar reconstruction and curvilinear reformatting. These techniques have been shown to improve the visual display of subtle lesions on MRI.[8] Gyral abnormalities on MRI are not an "all or none" phenomenon and require expertise and optimal images. Thick MRI slices would miss most of the abnormalities described here. The in vivo diagnosis of these cortical abnormalities casts new light on the physiopathology of DLD.

Many patients with DLD will end up having developmental dyslexia (DD), which implies difficulty in learning how to read and write despite normal intelligence, emotional stability, and adequate family and educational opportunities.[2,3] Dyslexia can be viewed as lying within a continuum of DLD.[9] Neuropathologic studies of the brains of two patients with DD and history of speech delay or language difficulty showed PMG involving the perisylvian region and left inferior frontal and superior temporal gyri.[3] This anatomical distribution coincides with our findings and corroborates that a cortical anomaly involving the perisylvian region plays an important role in the pathogenesis of DD and DLD.

Most of our patients presented with bilateral and symmetric cortical abnormalities, and only three children had asymmetrical lesions: two had bilateral perisylvian PMG with predominance in the left hemisphere, and one had unilateral PMG in the right frontal lobe. Our findings suggest that left-sided predominance of the lesions is not necessarily the rule in DLD, as has been proposed by others.[3,10] Indeed, most of our patients presented with symmetrical cortical abnormalities.

Our findings may represent a step further in the

*Table 2 Summary data of language assessment*

| Patient no. | Type of phonologic alteration | Syntax | Semantics (vocabulary and evocation) | Lexical reception (comprehension of sentences) | Pragmatics | Subtype |
|---|---|---|---|---|---|---|
| 1 | NA | NA | NA | Peabody: 60; short and long sentences: difficulty | Limited communicative ability | Global disorder |
| 2 | Delayed | Normal | Adequate vocabulary | Peabody: 110; normal | Normal | Phonologic programming disorder |
| 3 | Delayed | Normal | Adequate vocabulary | Peabody: 110; normal | Normal | Phonologic programming disorder |
| 4 | Delayed | Abnormal | Adequate vocabulary | Peabody: 84; normal | Normal | Phonologic programming disorder |
| 5 | Delayed Deviant | Abnormal | Restricted vocabulary | Peabody: 73; long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |
| 6 | Delayed | Abnormal | Restricted vocabulary; difficulty of evocation; use of periphrases | Peabody: 93; long sentences: difficulty | Limited communicative ability; prominent word-finding difficulty | Lexical–syntactic disorder |
| 7 | Inaccurate | Abnormal | Restricted vocabulary | Peabody: 85; short and long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |
| 8 | NA | NA | NA | Peabody: 80; short and long sentences: difficulty | Good communicative ability with RG | Global disorder |
| 9 | Inaccurate | Abnormal | Restricted vocabulary | Peabody: 78; long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |
| 10 | NA | NA | NA | Peabody: 55; short and long sentences: difficulty | Good communicative ability with RG | Global disorder |
| 11 | Inaccurate | Abnormal | Restricted vocabulary | Peabody: 70; short and long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |
| 12 | NA | NA | NA | Peabody: 55; short and long sentences: difficulty | Limited communicative ability | Global disorder |
| 13 | Inaccurate | Abnormal | Restricted vocabulary | Peabody: 70; long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |
| 14 | Delayed | Abnormal | Restricted vocabulary | Peabody: 72; long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |
| 15 | Delayed | Abnormal | Restricted vocabulary | Peabody: 80; short and long sentences: difficulty | Limited communicative ability | Phonologic–syntactic disorder |

NA = not applicable (no speech); RG = representative gesture.

understanding of the anatomical distribution of the cortical abnormalities in DLD. Patients with diffuse PMG around the entire sylvian fissure extending to the inferior frontal regions had a more severe clinical manifestation of DLD: they did not speak at all or had severe dysarthria. Conversely, those children whose PMG was limited to the posterior aspects of the parietal regions, without involvement of the anterior two-thirds of the sylvian fissure and frontal lobe, had milder or no dysarthria.

Children with language delay and pseudobulbar signs tend to fail at answering simple questions, and sometimes even drool. It is extremely important that the correct diagnosis of DLD be adequately applied because many patients may be perceived as mentally retarded. The wrong label and the stigma may impair their quality of life and may prevent them from attending regular schools.

The male predominance in our patients is a common finding[1,11] in DLD series. In one study that described 12 kindreds with familial perisylvian PMG, the authors concluded that this entity appears to be genetically heterogeneous.[12] However, most of the families provided evidence suggestive of or compatible with X-linked transmission, and this may be the explanation of the male predominance. Family his-

tory was a common finding in this study and this supports the belief that DLD may be genetically determined.[13-16]

The finding that eight of our patients presented mild motor delay and one had mild hemiparesis does not rule out DLD, as this term is applied when specific conditions involving mainly the language domain are considered. It is noteworthy that parents of our patients looked for medical assistance because of language delay and not for any other reason.

The complete clinical picture of perisylvian syndrome comprehends pseudobulbar palsy, cognitive deficits, epilepsy, and perisylvian abnormalities on imaging studies.[17,18] DLD has long been considered a manifestation of pseudobulbar paresis since the first descriptions of congenital suprabulbar paresis by Worster–Drought,[19-21] who presented a classification of speech disorders in children. Cognitive deficit is part of the syndrome, but in this study we included only individuals with normal or borderline cognitive function; otherwise, they could not be classified as having a specific developmental delay.

Epilepsy is considered to be a frequent symptom in patients with perisylvian PMG.[22,23] Seizures occurred in 87% of 31 patients with congenital bilateral perisylvian syndrome (CBPS),[22] which probably reflected a selective referral bias of patients seen at epilepsy surgery centers. In another series,[12] epilepsy occurred in 43% of patients; this series reflects a broader inclusion criteria. In the current study, although epilepsy was not an exclusion criterion, none of the patients had epilepsy. It is not unlikely, however, that a number of our patients may develop epilepsy in the future. The absence of seizures may be related to the fact that more than half of our children were 6 years old or younger. Patients with malformations of cortical development may not develop epilepsy until the second half of the first decade or even the second decade of life.[22]

We believe that when CBPS was first described, only patients presenting its severe form could be identified, and they indeed frequently presented epilepsy and cognitive disturbances. However, more recently, the advances in neuroimaging, especially high-resolution MRI and its postprocessing techniques, have enabled the diagnosis of more subtle forms of cortical abnormalities around the sylvian fissure. This reflects a much broader clinical picture of perisylvian syndrome than previously thought.

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**Variable Presentation and Severity of Epilepsy in the Different Types of Malformations of Cortical Development (Submetido)**

# Variable Presentation and Severity of Epilepsy in the Different Types of Malformations of Cortical Development

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**Key words**: Malformations of cortical development, EEG, epilepsy, childhood.

**Running title**: Epilepsy in MCD.

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## ABSTRACT

**Rationale:** Malformations of cortical development (MCD) usually manifest in childhood with epilepsy, developmental delay and focal neurological abnormalities. However, some patients may have near-normal cognitive function and no seizures. The objective of this study is to evaluate the variable presentation and severity of epilepsy in the different types of MCD.

**Methods:** We evaluated 100 consecutive patients with neuroimaging diagnosis of MCD. We assessed the occurrence of epilepsy, neurological examination and EEG findings. For analysis of the data, patients were divided into groups according to the type of MCD: focal cortical dysplasia, hemimegalencephaly, lissencephaly (agyria-pachygyria), subcortical laminar heterotopia, unilateral heterotopia, bilateral periventricular heterotopia, polymicrogyria and schizencephaly.

**Results:** There were 55 women, with ages ranging from 5 months to 71 years old (mean=15.2 years). All patients with hemimegalencephaly, unilateral periventricular heterotopia, subcortical laminar heterotopia and lissencephaly (agyria-pachygyria) had epilepsy. Epilepsy occurred also in 27/28 (96.5%) patients with focal cortical dysplasia, in 4/5 (80%) with bilateral periventricular nodular heterotopia, in 10/16 (62.5%) with schizencephaly, and in 13/28 (46.5%) with polymicrogyria. In patients with polymicrogyria and schizencephaly, seizures were less frequent ($p<0.001$) and more easily controlled by antiepileptic drugs ($p<0.001$). Regarding the type of epileptic syndrome, secondary generalized epilepsy occurred in 20% of the patients, especially when the lesion was diffuse ($p<0.001$). All of these 20 patients had their first seizure before 6 years-old.

The type of epileptiform abnormality varied according to the patient's age, depending on the degree of cerebral maturation

**Conclusion:** In a group of patients with MCD, the frequency of epilepsy is lower and seizures are more easily controlled in the setting of polymicrogyria and schizencephaly. Patients with MCD frequently present secondary generalized epilepsy early in childhood, especially when the lesion is diffuse.

Malformations of cortical development (MCD) can be defined as derangements in the development of the neocortex associated with a range of morphologic features and with multiple putative etiologic factors, including genetic and environmental influences [1]. The different types of MCDs are the result of abnormalities that occurred at different stages of cortical development [2].

The first dysplastic lesions described were anatomopathological findings, and only severely disabled patients could be identified [3]. With the improvement in neuroimaging techniques, smaller lesions have been described [4-5]. This led to the identification of patients presenting less severe symptoms than previously described.

Although MCD usually manifest in childhood with epilepsy, developmental delay and focal neurologic signs, some patients may have normal or near-normal cognitive function and no seizures [6]. Moreover, the identification of familial cases of MCD [7,8] and the understanding of its molecular basis [9-18] proved that the clinical spectrum of MCD is much wider than previously suspected.

The objective of this study is to describe the frequency of epilepsy, seizure control with antiepileptic drugs, and type of epileptic syndrome associated with the different forms of MCD.

## METHODS

We evaluated 100 consecutive patients with neuroimaging diagnosis of MCD. They were identified through a systematic investigation of patients seen at the neurology clinic of a tertiary hospital, at University of Campinas. Patients were evaluated even when

symptoms were mild, such as speech delay in childhood. All patients signed an informed consent obtained according to the declaration of Helsinki, and the protocol was approved by the ethical committee of our institution.

All patients were seen and examined by at least one of us. Clinical information was collected prospectively on follow-up visits, and by review of clinical notes. Investigation included neuroimaging evaluation, neurological examination, serial electroencephalograms (EEG) and long term video-EEG monitoring when appropriate.

We used a semi-structured questionnaire to assess the occurrence epilepsy, seizure control and age of first seizure. We also reviewed the clinical files of all patients.

For analysis of the data, patients were divided into groups according to the type of MCD: focal cortical dysplasia, hemimegalencephaly, unilateral periventricular heterotopia, bilateral periventricular nodular heterotopia, lissencephaly (agyria-pachygyria), subcortical laminar heterotopia, polymicrogyria, and schizencephaly.

We used the chi-square test to analyze the occurrence of epilepsy and seizure control among the different types of MCD. We considered the significance level of 0.05.

***MRI***

The diagnosis of MCD was established according to MRI findings. MRI was performed in a 2T scanner (Elscint Prestige, Haifa, Israel) using our epilepsy protocol: (*a*) *sagittal* T1 spin-echo, 6mm thick (TR=430, TE=12) for optimal orientation of the subsequent images; (*b*) *coronal* T1 inversion recovery, 3mm thick (flip angle=200°; TR=2800-3000, TE=14, inversion time TI=840, matrix=130X256, FOV=16X18 cm); (*c*)

*coronal* T2-weighted "fast spin echo" (FSE), 3-4mm thick, (flip angle=120°; TR=4800, TE=129, matrix=252X320, FOV=18X18cm), (*d*) *axial* images parallel to the long axis of the hippocampus; T1 gradient echo (GRE), 3mm thick (flip angle=70°, TR=200, TE=5, matrix=180X232, FOV=22X22 cm); (*e*) *axial* T2 FSE, 4mm thick, (flip angle- 120°, TR=6800, TE=129, matrix 252X328, FOV=21X23cm); (*f*) v*olumetric (3D)* T1 GRE, acquired in the sagittal plane for multiplanar reconstruction (MPR), 1 - 1.5mm thick (TA=35°, TR=22, TE=9, matrix=256X220, FOV=23X25cm). We performed MPR and curvilinear reformatting in all 3D MRI.

***EEG***

EEG recordings were performed routinely, using the International 10–20 system for electrode placement. EEG findings were classified as normal or abnormal. Only epileptiform abnormalities were considered, and could be focal or generalized.

We evaluated the type of EEG abnormalities according to the patient's age. For this purpose we considered only epileptiform abnormalities. The epileptiform abnormalities were classified in four types: a) high amplitude polyspikes and burst-suppression, or hypsarrhythmia, b) slow, <2.5Hz, spike-and-wave complexes (Lennox-Gastaut syndrome), c) focal, and d) generalized. Non-epileptiform abnormalities or EEG within normal limits were not included in this analysis. According to the patient's age, the type of EEG abnormality was plotted in a box plot graph.

*Type of epileptic syndrome*

The type of epileptic syndrome was classified according to the criteria proposed by the International League Against Epilepsy [19]. In order to evaluate if the extension of the MCD favored the occurrence of age-related secondary generalized epilepsy (West and Lennox-Gastaut syndromes), we evaluated the occurrence of secondary generalized epilepsy according to the type of lesion. For this analysis, patients were divided into groups according to the extension of lesion: diffuse (lissencephaly, subcortical laminar heterotopia, hemimegalencephaly) or focal (schizencephaly, polymicrogyria, focal cortical dysplasia, focal subcortical heterotopias).

Secondary generalized epilepsies are seen mostly in children due to their immature brain. In order to assess the profile of this type of epileptic syndromes in childhood, we performed a separate analysis of the patients in whom seizures started before 6 years of age.

## RESULTS

There were 55 women, with ages ranging from 5 months to 71 years old (mean=15.2 years). Twenty-eight patients had focal cortical dysplasia, 28 polymicrogyria, 16 schizencephaly, nine lissencephaly (agyria-pachygyria), five subcortical laminar heterotopia, five unilateral heterotopia, five bilateral periventricular nodular heterotopia, and four hemimegalencephaly.

*Frequency of epilepsy*

All patients with hemimegalencephaly, unilateral periventricular heterotopia, subcortical laminar heterotopia and lissencephaly (agyria-pachygyria) had epilepsy. Epilepsy occurred also in 27/28 (96.5%) of the patients with focal cortical dysplasia, in 4/5 (80%) with bilateral periventricular nodular heterotopia, in 10/16 (62.5%) with schizencephaly, and in 13/28 (46.5%) with polymicrogyria. Epilepsy was less frequent in patients with polymicrogyria and schizencephaly ($p<0.001$).

*Seizure control with AED*

No patient with subcortical laminar heterotopia and hemimegalencephaly had their seizures controlled with antiepileptic drugs (AED). Seizures were controlled in 1/28 (3%) of patients with focal cortical dysplasia, in 1/9 (11%) with lissencephaly (agyria-pachygyria), in 1/5 (20%) with unilateral heterotopia, in 1/5 (20%) with bilateral periventricular nodular heterotopia, in 5/13 with (38.5%) with polymicrogyria and in 7/10 (70%) with schizencephaly. Patients with schizencephaly and polymicrogyria had their seizures more easily controlled by AED ($p<0.001$).

*Type of epileptic syndrome*

From the group of 100 patients, 78 presented epilepsy. Sixty-one had partial epileptic syndromes, 13 secondary generalized syndromes, and in 3 the type of epileptic syndrome could not be established.

Twenty patients presented secondary generalized epilepsy during the first decade of life. Every patient with secondary generalized epilepsy presented their first seizure before 6 years of age. Seven patients with secondary generalized epilepsy developed partial seizures in the second decade of life, characterizing a partial epileptic syndrome. No patient with partial epilepsy developed a secondary generalized epileptic syndrome.

Among the 20 patients who presented a secondary generalized epileptic syndrome, 6/9 had lissencephaly (agyria-pachygyria), 2/2 had subcortical laminar heterotopia, 3/4 had hemimegalencephaly, 2/19 had focal cortical dysplasia, 4/8 had schizencephaly, 1/4 had focal heterotopias and 2/8 had polymicrogyria.

Figure 1 shows the type of epileptic syndrome according to the type of MCD: focal or diffuse. Secondary generalized epilepsy was more frequently seen in patients with diffuse MCD (hemimegalencephaly, lissencephaly and subcortical laminar heterotopia; [p=0.004]).

***Type of epileptic syndrome when seizures started before 6 years of age.***

Fifty-four patients presented their first seizure before six years-old. Among them, 20 (37%) presented a secondary generalized epileptic syndrome. Fifteen had diffuse and 39 focal MCD.

According to the extension of the lesion, 73% (11/15) of the patients with diffuse lesion (lissencephaly, subcortical laminar heterotopia and hemimegalencephaly) presented secondary generalized epilepsy, as opposed to only 23% (9/39) in the group with focal

lesion (focal cortical dysplasia, periventricular nodular heterotopia, unilateral heterotopias, polymicrogyria and schizencephaly; [$p<0.001$]).

***EEG and neurological examination***

Type of seizure, age of the first seizure, EEG characteristics, and the findings of neurological examination are shown on table 1 and 2. It is interesting to note that in 22% of the patients the EEG was normal and 38% had normal neurological examination.

Electroencephalographic evaluation was performed (1 to 5 recordings) in all but one patient with schizencephaly, one with periventricular nodular heterotopia and 10 patients with polymicrogyria. These patients without EEG evaluation did not have epilepsy.

Figure 2 shows the type of EEG abnormality according to the patient's age. A total of 134 abnormal EEG recordings were included in this analysis.

***EEG in patients without epilepsy***

Twenty-one patients never had seizures. EEG was performed in 12 patients without epilepsy (six with polymicrogyria and six schizencephaly). EEG was normal in seven patients, and presented epileptiform abnormalities in five.

## DISCUSSION

The diagnosis of MCD is usually considered in severely disabled patients, especially in the setting of refractory epilepsy. However, some patients have normal, or near normal, cognitive function and no seizures [6]. Although many patients with MCD presenting in childhood have often more severe clinical manifestations [20], we found a normal neurological examination in 33% of the patients (table 2). These patients were identified through a systematic investigation where a MRI was performed even when symptoms were mild.

Epilepsy is frequently seen in patients with MCD and a characteristic EEG pattern consisting of rhythmic epileptiform activity has been described [21]. It is important to note that although focal cortical dysplasia has intrinsic epileptogenecity [22, 23], normal EEG findings should not preclude the diagnosis of MCD in patients with epilepsy. We found 22% of the patients with normal EEG findings, including 2/28 (7%) with focal cortical dysplasia.

The type of seizure associated to MCD can be variable, and the patient's age is one of the most import aspects in the determination of the epileptic syndrome. Epileptic syndromes in the first three months of life are characterized by burst-suppression, which reflects the dysfunction of thalamo-cortical connections. West syndrome is characterized by infantile spasms, hypsarrthymia and developmental delay, and is seen mainly from the forth to the seventh months of life. The age range of expression of hypsarrhythmia correlates with the differentiation of the intracortical synchronizing mechanism provided

by intrinsically bursting neurons. In the second year of life there is sufficient degree of maturation to support sustained rhythmic discharges of spikes and waves. Lennox-Gastaut syndrome is the clinical expression of this age [24]. The electroencephalographic evaluation of our patients showed that the pattern of EEG abnormalities present in patients with MCD reflects clearly these three main stages of cerebral maturation (figure 2). Hypsarrhythmia occurred in the first year of life. Generalized epileptiform activity characterized by slow, <2.5Hz, spike-and-wave complexes were seen mainly in the first decade of life. Focal and generalized epileptiform activities were seen throughout life.

EEG findings of patients with MCD are often stable over time and some patients may development slow waves or interictal spikes when followed serially for several years[25]. However, our data shows that, in childhood, the type of EEG finding depends mostly on the patient's age; that is, the type of epileptiform abnormality changes according to degree of cerebral maturation (myelinization and synaptogenesis).

It is interesting to note that, although most patients with epilepsy due to MCD show interictal spikes [25], we found epileptiform abnormalities in 42% (5/12) of the patients without epilepsy.

Secondary generalized epilepsy occurred in 20% of patients with MCD, especially when the dysplastic lesion was diffuse (p=0.004). MCD is the most common cause of partial seizures in childhood [26]. However, it is interesting to note that 23% (9/39) of the children with a focal lesion presented secondary generalized epilepsy. One of our patients with focal cortical dysplasia presented West syndrome in the first months of life and became seizure free after AED treatment. Motor and cognitive developments were normal.

His seizures restarted at age nine and at this time were partial, delineating the age dependent expression of the epileptic syndrome.

The frequency of epilepsy was lower ($p<0.001$) and seizures were more easily controlled ($p<0.001$) in patients with polymicrogyria and schizencephaly. These findings are in agreement with previous studies in which epilepsy was present in 57% to 87% of patients with polymicrogyria or schizencephaly [27-31]. It is also in keeping with our previous findings from a smaller series [32]. In these studies the epileptic spectrum was wide and most patients had a good seizure outcome. It should be noted that, because MCD are frequently associated with refractory epilepsy, most data about epilepsy and MCD comes from epilepsy centers. In order to avoid this bias, we performed a systematic neuroimaging evaluation of patients seen at our neurology clinic, and it enabled the identification of a higher number of patients with MCD that did not present epilepsy. However, we believe that the frequency of epilepsy in patients with MCD is still underestimated, because nearly asymptomatic patients with MCD can not be identified because they will not seek medical help.

We conclude that in a group of patients with MDC, the frequency of epilepsy is lower and seizures are more easily controlled in patients with polymicrogyria and schizencephaly. Patients with MCD frequently present secondary generalized epilepsy early in childhood (before six years of age), especially when the lesion is diffuse.

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**Table 1 - Characteristics of epilepsy according to the different types of malformations of cortical development.**

| Type of MCD | Epilepsy | Seizures controlled with AED | Mean age of first seizure | Type of seizure* |
|---|---|---|---|---|
| Focal cortical dysplasia (n=28) | 27/28 (96.5%) | 1/27 (3%) | 4.6 years | Partial - 100% |
| Hemimegalencephaly (n=4) | 4/4 (100%) | None | 2 months | Partial- 100%<br>Generalized - 25% |
| Bilateral periventricular nodular heterotopia (n=5) | 4/5 (80%) | 1/4 (25%) | 13.2 years | Partial - 75%<br>Generalized - 25% |
| Unilateral periventricular heterotopia (n=5) | 5/5 (100%) | 1/5 (20%) | 13.1 years | Partial - 100% |
| Subcortical laminar heterotopia (n=5) | 5/5 (100%) | None | 8.4 years | Partial - 75%<br>Generalized - 25% |
| Agyria-pachigyria (n=9) | 9/9 (100%) | 1/9 (11%) | 6 months | Partial - 33%<br>Generalized - 55.5% |
| Polymicrogyria (n=28) | 13/28 (46.5%) | 5/13 (38.5%) | 8.8 years | Partial - 54%<br>Generalized - 15% |
| Schizencephaly (n=16) | 10/16 (62.5%) | 7/10 (70%) | 4 years | Partial - 70%<br>Generalized - 30% |

AED = antiepileptic drugs. * Some patients presented more than on type of seizure, neurological abnormality or EEG finding.

**Table 2 - Clinical characteristics and EEG findings, according to the different types of malformations of cortical development.**

| Type of MCD | Neurological examination* | EEG findings* |
|---|---|---|
| Focal cortical dysplasia (n=27) | Normal - 75%<br>MR - 10%<br>Hemianopsia - 7%<br>MD - 3% | Focal – 21 /28 (75%)<br>Generalized – 7/28 (25%)<br>Normal – 2/28 (7%)<br>RED – 9 (32%) |
| Hemimegalencephaly (n=4) | MD - 100%<br>MR - 100% | Focal – 4/4 (100%)<br>RED -1/4 (25%) |
| Bilateral periventricular nodular heterotopia (n=5) | Normal - 80%<br>MR - 20% | Focal – 1/4 (25%)<br>Generalized – 1/4 (25%)<br>Normal – 2/4 (50%) |
| Unilateral periventricular heterotopia (n=5) | Normal - 80%<br>MR - 20% | Focal – 1/4 (25%)<br>Generalized – 2/4 (50%)<br>Normal – 2/4 (50%) |
| Subcortical laminar heterotopia (n=5) | Normal - 40%<br>MR - 40%<br>MD - 20% | Focal – 5/5 (100%)<br>Generalized – 2/5 (40%) |
| Agyria-pachigyria (n=9) | MD - 55.5%<br>MR - 55%<br>Hypotonia - 33%<br>VA - 22%<br>Microcephaly- 11% | Focal – 5/9 (55%)<br>Generalized – 7/9 (78%)<br>Normal – 1/9 (11%) |

MD = motor deficit; MR = mental retardation; VA= visual abnormalities; RED = rhythmic epileptiform discharge. * Some patients presented more than on type of seizure, neurological abnormality or EEG finding.

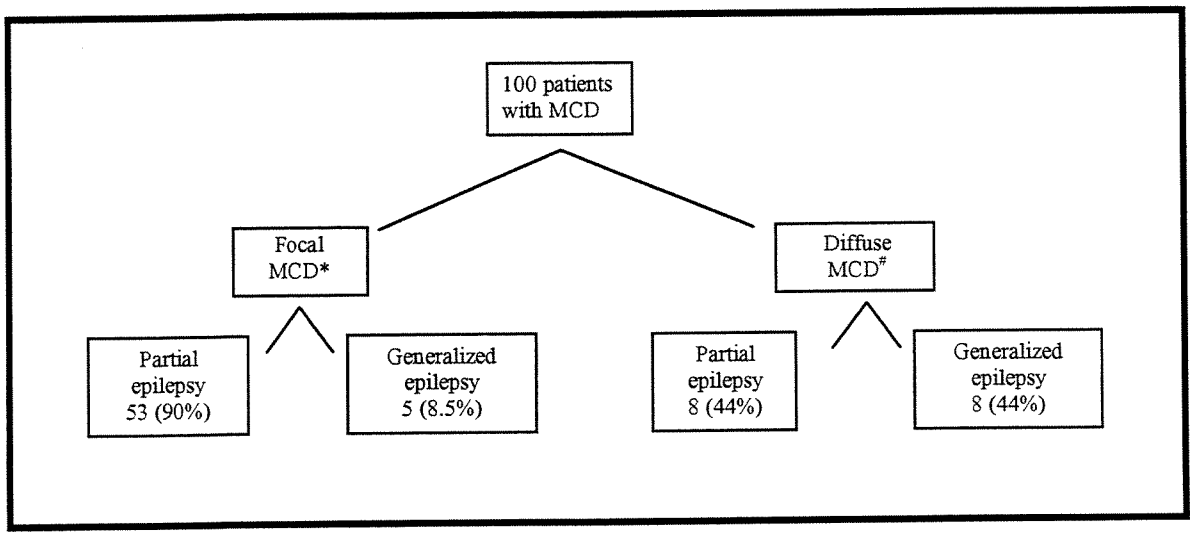
**Table 2 - Continued**

| Type of MCD | Neurological examination* | EEG findings* |
|---|---|---|
| Polymicrogyria (n=28) | PBP- 36%<br>Speech delay - 28.5%<br>MD - 28.5%<br>Normal - 25%<br>MR - 7%<br>Hypotonia - 3%<br>Microcephaly - 3% | Focal – 6/16 (37.5%)<br>Generalized – 3/16 (19%)<br>Normal – 10/16 (62.5%) |
| Schizencephaly (n=16) | MD - 50%<br>MR - 50%<br>VA - 20%<br>PBP - 10%<br>Microcephaly - 10% | Focal – 11/15 (73%)<br>Generalized –4/15 (27%)<br>Normal – 5/15 (30%) |

PBP = Pseudobulbar palsy, MD = motor deficit; MR = mental retardation; VA= visual abnormalities; RED = rhythmic epileptiform discharge. * Some patients presented more than on type of seizure, neurological abnormality or EEG finding.

## FIGURES

**Figure 1** - Type of epileptic syndrome according to the type of MCD: focal or diffuse.




Obs. In three patients (one with focal and two with diffuse MCD) the type of epileptic syndrome could not be established.
* Focal cortical dysplasia, nodular heterotopia, polymicrogyria or schizencephaly.
# Lissencephaly, subcortical laminar heterotopia and hemimegalencephaly.

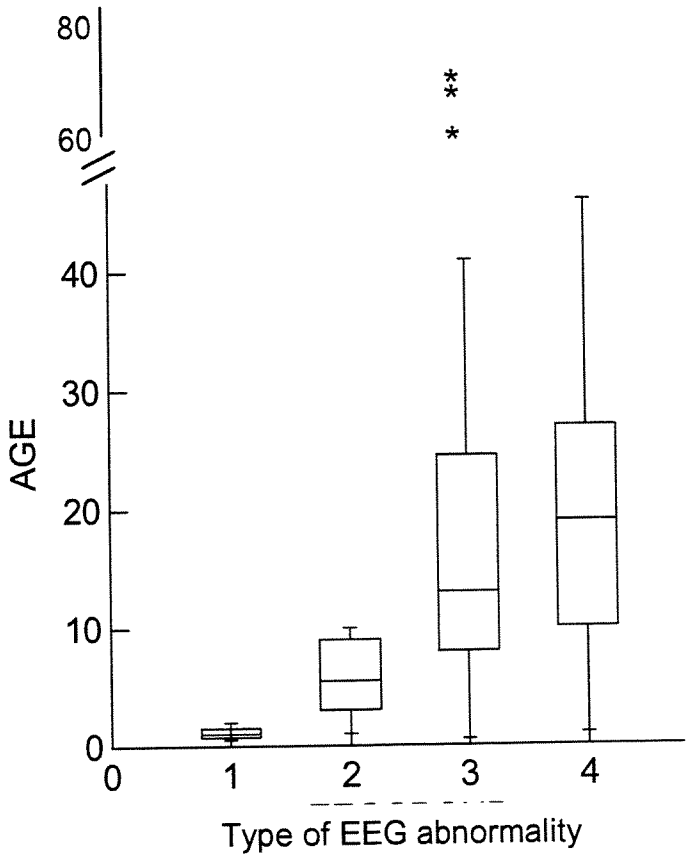



**Figure 2** - Epileptiform abnormalities according to the patient's age. Type of EEG abnormality: 1–Hypsarrhythmia; 2–Slow spike-and-wave complexes, <2.5Hz; 3–Focal epileptiform abnormality; 4–Generalized epileptiform abnormality. Note that hypsarrhythmia occurs mostly in the first year of life, and slow spike-and-wave complexes predominate in the first decade.

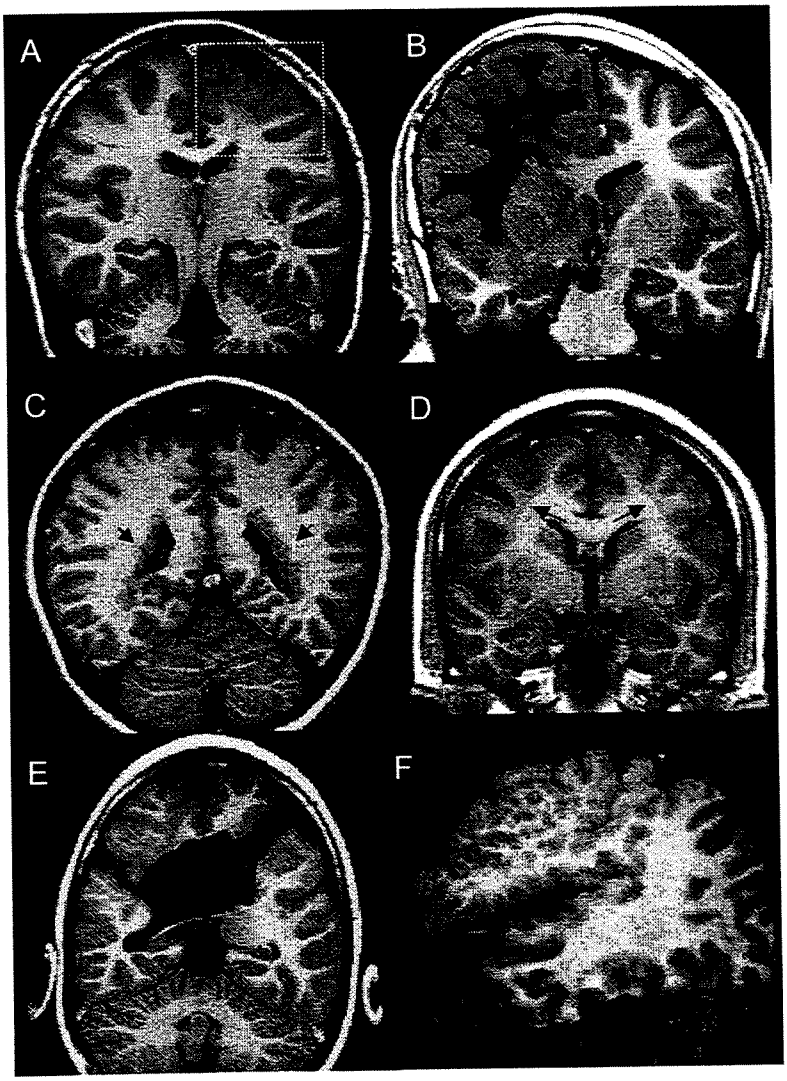



**Figure 3** – (A) Coronal T1-IR image showing area of cortical thickening and blurring between the gray and white matter in a patient with focal cortical dysplasia (box). (B) Coronal T1-IR image showing hemispheric enlargement with abnormal gyration, cortical thickening and abnormal white matter signal in a patient with hemimegalencephaly. (C) Coronal T1-IR image showing nodules around the ventricular wall, bilaterally, in a patient

with periventricular nodular heterotopia (arrows). (D) Coronal T1-IR image showing pachigyria and subcortical laminar heterotopia (arrows). (E) Coronal T1-IR image showing bilateral clefts in a patient with schizencephaly. (F) Sagittal T1 image showing polymicrogyria at the right frontal lobe.

# Capítulo IV

## Aspectos de neuroimagem das malformações do desenvolvimento cortical

Artigo 7 – Neuroimaging characteristics of pseudo-subcortical laminar heterotopia

Artigo 8 – Focal cortical dysplasia: improving diagnosis and localization with MRI curvilinear and multiplanar recosntruction

Artigo 9 – Patterns of hippocampal abnormalities in malformations of cortical development

**Neuroimaging Characteristics of Pseudo-Subcortical Laminar Heterotopia**

*J Neuroimaging 2002; 12: 52-54.*

# Short Communication

# Neuroimaging Characteristics of Pseudosubcortical Laminar Heterotopia

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## ABSTRACT

Subcortical laminar heterotopia (SLH) is a subtype of malformation of cortical development characterized by laminar gray matter between the cortex and ventricles, which can vary in thickness and may be continuous or discontinuous. The objective of this study is to describe a normal finding of high-resolution magnetic resonance imaging that may simulate an SLH. SLH is isointense to cortex on both T1- and T2-weighted/FLAIR images, usually both anteriorly and posteriorly in location. Conversely, pseudo-SLH is a normal variant present only at the posterior aspect of the brain, and with dark signal on both T1- and T2-weighted/FLAIR images.

Key words: Subcortical laminar heterotopia, normal variant, epilepsy, magnetic resonance imaging.

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The advent of magnetic resonance imaging (MRI) has enabled the in vivo display of lesions, such as malformations of cortical development (MCDs), that in the past could only be seen in pathological examinations.[1,2]

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MCDs constitute a group of heterogeneous lesions with presumed distinct underlying pathophysiology. Subcortical laminar heterotopia (SLH) is a subtype of MCD characterized as laminar gray matter between the cortex and ventricles, which can vary in thickness and may be continuous or discontinuous (Fig 1).

High-resolution MRI provides high contrast and anatomical definition of brain structures, and some normal aspects that were not usually seen on conventional images can be identified. On T1-weighted images, a thin layer isointense to gray matter may be observed, bilaterally, next to the trigone, and sometimes this may resemble SLH.

The objective of this study is to describe a normal finding of high-resolution MRI that may simulate an SLH.

## Methods

We analyzed high-resolution MRI and multiplanar reconstruction (MPR) of 20 normal controls and 4 patients with SLH. We were aware of whether the films belonged to controls or patients at the time of the analysis. MRI was performed on a 2.0-T scanner (Elscint Prestige) using our epilepsy protocol: (1) sagittal T1 spin echo, 6 mm thick (TR = 430, TE = 12), for optimal orientation of the subsequent images; (2) coronal T1 inversion recovery, 3 mm thick (flip angle = 200°, TR = 2800-3000, TE = 14, TI = 840, 130 × 256 matrix size, field of view = 16 × 18 cm); (3) coronal T2-weighted fast spin echo, 3 to 4 mm thick (flip angle = 120°, TR = 4800, TE = 129, 252 × 320 matrix size, field of view = 18 × 18 cm); (4) axial images parallel to the long axis of the hippocampi, T1 gradient echo, 3 mm thick (flip angle = 70°, TR = 200, TE = 5, 180 × 232 matrix size, field of view = 22 × 22 cm); (5) axial T2 FSE, 4 mm thick (tip angle 120°, TR = 6800, TE = 129, 252 × 328 matrix size, field of view = 21 × 23 cm); and (6) volumetric (3-dimensional) T1 GRE, acquired in the sagittal plane for

blurring between gray and white matter, and cortical thickening or infolding.[4,5]

SLH is characterized as a layer of gray matter observed in the centrum semi ovale, which extends to anterior regions of brain, at times associated with pachygyria. Patients with SLH usually present cognitive impairment and epilepsy, depending on the band thickness.[6] Pseudo-SLH cannot be seen in the anterior regions of the brain and is relatively thinner and closer to the lateral ventricles when compared to the actual SLH. An important aspect is that in FLAIR and T2-weighted sequences, only the truly abnormal SLH has a signal similar to cortex.

Pseudo-SLH, a normal subcortical structure, appears isointense to the cortex on T1-weighted sequences and may be misinterpreted as abnormal. This normal variant is due to the fact that the axons of the optic radiation are darker than other subcortical structures due to the presence of iron, which attenuates the MRI signal.[7] Optic radiation takes an indirect course from the lateral geniculate nucleus (around the lateral ventricle) to reach the primary visual cortex in the occipital lobe, and the improvement of MRI resolution enabled its clear visualization, giving the impression of pseudo-SLH.

We conclude that the diagnosis of SLH requires the observation of MRI signal isointense to cortex on both T1- and T2-weighted/FLAIR images, usually both anteriorly and posteriorly in location. Conversely, pseudo-SLH is a normal variant present only at the posterior aspect of the brain, with a dark signal on both T1-weighted and T2-weighted/FLAIR images.

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**Focal Cortical Dysplasia: Improving Diagnosis and Localization with MRI Curvilinear and Multiplanar Reconstruction**

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# Focal Cortical Dysplasia: Improving Diagnosis and Localization With Magnetic Resonance Imaging Multiplanar and Curvilinear Reconstruction

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## ABSTRACT

*Objective.* To establish the contribution of multiplanar reconstruction (MPR) and curvilinear reformatting (CR) to the MRI investigation of focal cortical dysplasia (FCD). *Methods.* From a group of patients with intractable frontal lobe epilepsy, we selected patients with neuroimaging diagnosis of FCD. The diagnosis of FCD was based on the neuroimaging findings after a three step evaluation, always in the same order: (a) plain MRI films, (b) MPR, and (c) CR. After the selection of patients, the process of reviewing all the images in the three stages described above was performed by one of us, who did not take part on the selection of patients nor on the initial evaluation, and who was blind to the clinical and EEG findings of the patients. For data analysis, we first assessed the contribution of the additional findings of MPR analysis compared to the results of the evaluation using only plain MRI films, as is usually done in routine practice. Second, we assessed the contribution of CR to the findings of plain MRI films plus MPR. After completing the multistep evaluation, we all went back to review the plain MRI films with knowledge of lesion topography, in order to identify possible subtle features associated with FCD. *Results.* Seventeen patients met the inclusion criteria. Twelve had imaging diagnosis of FCD and were included in the second step of this project. Plain films of high resolution MRI showed the lesion in 6 (50%) of the 12 patients. By adding MPR to the plain MRI films, we identified lesions in all 12 patients. Furthermore, we found that MPR provided a better lesion localization and ascertainment of its relationship to other cerebral structures in 5 of 6 (83%) patients who had a lesion identified on plain films. By adding CR to the plain MRI films plus MPR analysis, we observed that (a) CR also allowed the identification of the dysplastic lesion in all patients, (b) CR improved lesion localization in one patient, and (c) CR provided a better visualization of the lesion extent in 4 patients (33%), showed a larger lesion in 3, and demonstrated that part of the area suspected as abnormal was more likely volume averaging in 2. *Conclusion.* MPR and CR analysis add to the neuroimaging evaluation of FCD by improving the lesion diagnosis and localization. CR helps to establish the extent of the lesion more precisely, allowing the visualization of some areas not shown on high resolution MRI and MPR. These techniques are complementary and do not replace the conventional wisdom of MRI analysis.

Key words: Curvilinear reformatting, multiplanar reconstruction, focal cortical dysplasia, frontal lobe epilepsy.

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Focal cortical dysplasia (FCD) can be identified on conventional magnetic resonance imaging (MRI) as areas of abnormal gyration, blurring between gray and white matter, and cortical thickening or infolding that may be associated with clusters of heterotopic neurons in the white matter.[1–4] However, sulcal and cortical morphologic abnormalities are particularly difficult to diagnose unless a high index of suspicion is maintained.[5] At times, FCD may be very small and subtle, which makes it difficult to be detected on plain MRI films.[6,7] For this reason, high-resolution MRI and image-postprocessing techniques, such as multiplanar reconstruction (MPR) and curvilinear reformatting (CR), were developed.[6–10]

MPR is an interactive analysis of a volumetric acquisition that enables the observation in detail of specific cerebral regions in different orientations of plane of section. Barkovich et al[7] used 3-dimensional (3D) Fourier transform volumetric MRI examinations with thin (1 to 1.5

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mm) slices to evaluate 15 patients with previously normal neuroimaging evaluation and identified focal cortical abnormalities in 8 of these patients.

CR is an elegant approach that can easily distinguish subtle lesions from volume-averaging effect. CR is designed to avoid the impression of cortical thickening that can be seen in thick MRI slices. This artifact is due to the obliquity of the plane of section in relation to the gyrus, causing volume averaging.[10]

The objective of this study was to establish the contribution of MPR and CR to the MRI investigation of FCD and establish the degree of concordance among results from plain MRI, MPR, and CR with regard to the diagnosis, ascertainment of anatomical location, and extent of FCD.

## Patients and Methods

*Selection of Patients*

From January 1998 to January 2000, we selected patients with clinical and electroencephalogram (EEG) diagnosis of frontal lobe epilepsy refractory to medical treatment, and with no evidence of progressive metabolic disorder. Patients with tumors, inflammatory or destructive lesions, and other types of cortical dysgenesis were excluded. All patients had high-resolution MRI following a specific protocol, detailed below.

Patients went through a complete neuroimaging evaluation that included the analysis of plain MRI, MPR, and CR. Plain MRI included 6 mm sagittal T1, 3 mm coronal IR and T2, and 3 mm axial T1 gradient echo (GRE), T2, and FLAIR images, followed by MPR and CR on volumetric T1 1 to 1.5 mm isotropic voxel acquisition.

In the first step of the project, patients with FCD were identified. The diagnosis of FCD was made in the light of seizure semiology, neurophysiology, and neuroimaging findings.

*Neuroimaging Evaluation of Patients With FCD*

After the first selection of patients, the patients with FCD were reevaluated by one of the authors, who did not take part in the selection of patients and was blind to the clinical and EEG findings. The entire process of reviewing all the images was performed in the same 3 stages: (1) plain MRI, (2) MPR, and (3) CR.

**MRI.** MRI was performed in a 2.0-T scanner (Elscint Prestige, Haifa, Israel) using our epilepsy protocol: (1) sagittal T1 spin echo 6 mm thick (TR = 430, TE = 12, 1 NEX, 16 slices) for optimal orientation of the subsequent images; (2) coronal T1 inversion recovery 3 mm thick (flip angle = 200°, TR = 2800-3000, TE = 14, TI = 840, matrix = 130 × 256, FOV = 16 × 18 cm, 1 NEX, 30 slices); (3) coronal T2-weighted fast spin echo (FSE) 3 to 4 mm thick (flip angle = 120°, TR = 4800, TE = 129, matrix = 252 × 320, FOV = 18 × 18 cm, 1 NEX, 24 slices); (4) axial images parallel to the long axis of the hippocampi, T1 GRE 3 mm thick (flip angle = 70°, TR = 200, TE = 5, matrix = 180 × 232, FOV = 22 × 22 cm, 4 NEX, 24 slices); (5) axial T2 FSE 4 mm thick (flip angle = 120°, TR = 6800, TE = 129, matrix 252 × 328, FOV = 21 × 23 cm, 1 NEX, 24 slices); (6) axial IRFSE-FLAIR 5 mm thick (TR = 2550, TE = 90, matrix = 250 × 250, FOV = 24 × 24 cm, 1 NEX, 24 slices); and (7) volumetric (3D) T1 GRE, acquired in the sagittal plane for MPR 1 to 1.5 mm thick (flip angle = 35°, TR = 22, TE = 9, matrix = 256 × 220, FOV = 23 × 25 cm, 1 NEX, 170 to 200 slices according to the size of the patient's head). Total scanning time was 45 to 60 minutes.

**MPR.** MPR was performed in a workstation (O2 Silicon Graphic) using Omnipro software (Elscint Prestige, Haifa, Israel), which allowed a fast reconstruction of MRI in any plane. Both T1- and T2-weighted images were loaded in the workstation to assist in the detection of abnormalities.

**CR.** CR of 3D volumetric images was performed in a Power MacIntosh using Brainsight software (Rogue Research, Montreal, Quebec, Canada). This is a method that improves the anatomical display of the gyral structure of the hemispheric convexities. It also reduces the asymmetric sampling of gray-white matter that may lead to false-positive results.

*Analysis of the Data*

We analyzed the results in 2 stages. First, we assessed the contribution of additional findings of MPR analysis compared to the results of the evaluation using only plain MRI, as is usually done in routine practice. Second, we assessed the contribution of CR to the findings of plain MRI plus MPR. For comparison of the extent of FCD between MPR and CR results, the lesion shown by MPR was manually delineated and then compared directly to the 3D curvilinear image in an interactive manner, using the cursor of CR software (Fig 1). The same investigator performed all 3 steps of the analysis, always in the same order—(1) plain MRI, (2) MPR, and (3) CR—in the same way it was performed in the first step of the project when patients diagnosed with FCD were selected.

After completing the multistep evaluation, we went back to review the plain MRI with knowledge of lesion topography in order to identify possible subtle features associated to FCD. These features could be helpful as clues in the routine evaluation of patients with partial epilepsy.

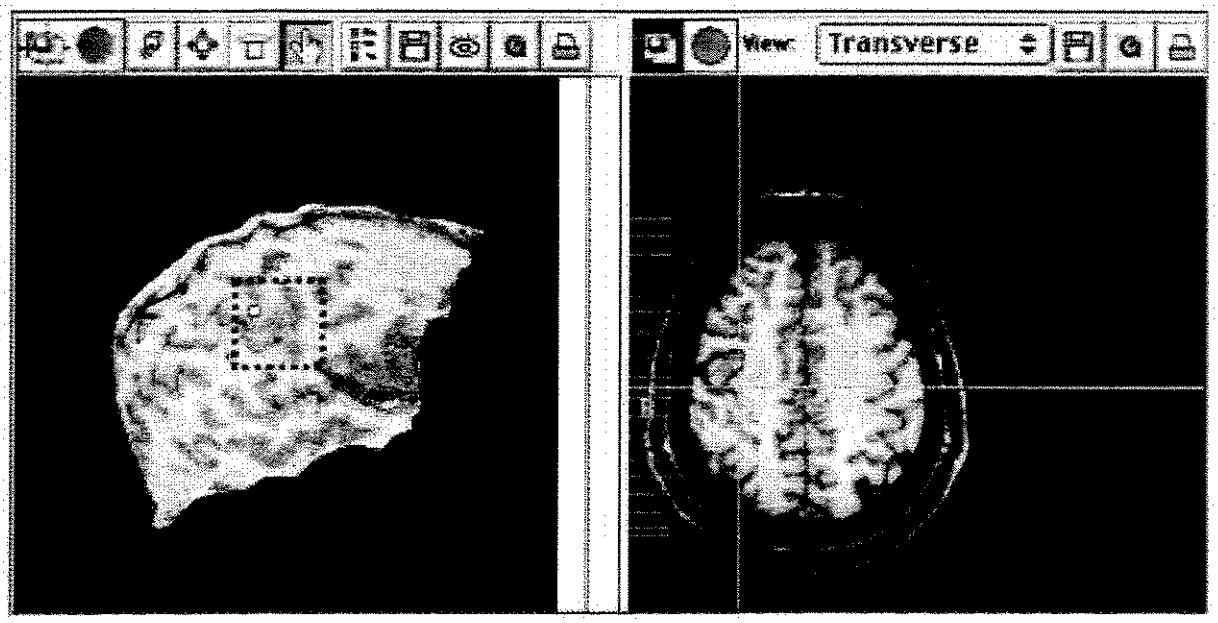


**Fig 1.** (A) Curvilinear reformatting at 16 mm of depth from the cortical surface shows a dysplastic lesion (within the box). The dot indicates the limit of the dysplastic lesion on the curvilinear reformatting image. (B) Axial T1-weighted image shows the dysplastic lesion in the right frontal region, and the limits of the lesion are contoured in black. Note that the cross-lines, which correspond to the exact position of the dot in (A), fall outside the limits of multiplanar reconstruction–defined lesion.

## Results

Initially, 17 patients met the inclusion criteria of clinical-EEG diagnosis of frontal lobe epilepsy refractory to medical treatment. After the first systematic MRI analysis, the diagnosis was uncertain in 5 patients, and 12 had imaging diagnosis of FCD. These 12 patients were included in the second step of the project in order to determine the contribution of each postprocessing MRI technique for the diagnosis of FCD.

Ages ranged from 2 to 41 years (mean = 13). Neurological examination was normal in all but 3 patients, who presented with only mild abnormalities such as asymmetry of nasolabial folds (patients 1 and 7) and lower facial weakness and speech delay (patient 10). All patients had seizures suggesting frontal lobe involvement. EEG showed focal epileptiform abnormalities in 8 patients, generalized epileptiform abnormalities in 2 patients, and focal plus generalized epileptiform abnormalities in 2 patients. Seven patients presented with focal rhythmic epileptiform discharges in their EEGs (Table 1).

The time required to perform MPR is variable, and may last up to 2 hours. CR is faster—the time required to delineate the brain surface is approximately 5 minutes and the generation and display of curves takes about 8 to 10 minutes.[10] The analysis of the results, however, varies from patient to patient, and in our study it required approximately 20 to 30 minutes for each patient.

In the first analysis of plain MRI, we found a lesion with confidence in only 6 of the 12 patients included in the second step of the study. By adding MPR to the plain films of conventional high-resolution MRI, we identified lesions in all 12 patients. Furthermore, we found that MPR provided a better lesion localization and ascertainment of its relationship to other cerebral structures in 5 of 6 (83%) patients who had a lesion identified on plain films. The possibility of changing the plane of section with different angulations and the ability to observe the influence of these changes simultaneously in 3 or more planes of section is extremely helpful to rule out volume averaging in MPR (Fig 2).

When the results of the CR analysis were compared to the findings of plain MRI plus MPR analysis, we observed that (1) CR also allowed for the identification of the dysplastic lesion in all patients; (2) CR improved lesion localization in 1 patient; and (3) CR provided a better visualization of the lesion extent in 4 patients (33%), showed a larger lesion in 3 patients (patients 4, 5, and 6) (Fig 1), and demonstrated that part of the area suspected as abnormal was more likely volume averaging in 2 (patients 6 and 7) (Fig 3).

Table 1. Characteristics of Electroencephalogram (EEG), Seizure Semiology, and Neuroimaging Findings of Patients With Focal Cortical Dysplasia

| ID | Age/Sex | EEG | Seizure Semiology | Location of Focal Cortical Dysplasia |
|---|---|---|---|---|
| 1 | 7/M | Rhythmic epileptiform discharges at left frontal region | Paresthesia on the right hand, followed by tonic posture of right arm and lip protrusion | Left postcentral gyrus[a] |
| 2 | 21/F | Generalized spike and wave | Tonic posture of arms followed by complex partial seizure | Right middle frontal gyrus |
| 3 | 12/M | Rhythmic epileptiform discharges at right frontal region | Clonic movements of right lower face, followed by complex partial seizure | Left superior and middle frontal gyrus[a] |
| 4 | 4/F | Bilateral spikes at frontotemporal regions | Right eye blink followed by complex partial seizure | Right precentral gyrus |
| 5 | 10/M | Focal spikes at right frontocentral regions | Complex partial seizure characterized by staring and automatisms | Right middle frontal gyrus[a] |
| 6 | 41/F | Frontal spikes at right frontal region and generalized spike and wave | Loss of consciousness followed by bizarre movements and tonic posture of arms | Right middle frontal gyrus[a] |
| 7 | 8/F | Rhythmic epileptiform discharges at left frontal region | Tonic deviation of right side of lower face and tonic posture of right arm | Left precentral gyrus[a] |
| 8 | 3/F | Rhythmic epileptiform discharges at left frontal region | Clonic movements of right arm | Left precentral gyrus |
| 9 | 4/F | Rhythmic epileptiform discharges at right frontocentral regions and generalized spike and wave | Clonic movement of left arm and leg | Right precentral gyrus |
| 10 | 2/M | Rhythmic epileptiform discharges at frontotemporal regions | Bilateral eye blinking with loss of consciousness, followed by generalized tonic-clonic seizure | Right middle and inferior frontal and superior temporal gyrus[a] |
| 11 | 14/M | Generalized spike and wave | Postural seizure (extension of 4 limbs) | Right middle frontal gyrus |
| 12 | 26/F | Focal spikes at right frontal region | Loss of consciousness followed by generalized tonic-clonic seizure | Left middle frontal gyrus |

a. Focal cortical dysplasia was visible with confidence in plain magnetic resonance imaging.

A retrospective analysis of plain MRI previously considered as normal revealed some specific features that were present in all 12 patients.

- An area of possible focal cortical thickening that can be seen in at least 3 sequential thin slices (≤ 3 mm) in plane, which was present in all patients;
- A suspicious area seen in both coronal and axial sequences (present in 11 of 12 patients);
- Focal tissue loss (present in 10 of 12 patients);
- A sulcus that is deeper or straighter than usual (present in 9 of 12 patients);
- Focal hyperintense signal on T2-weighted or FLAIR images (present in 5 of 12 patients) (Figs 4, 5).

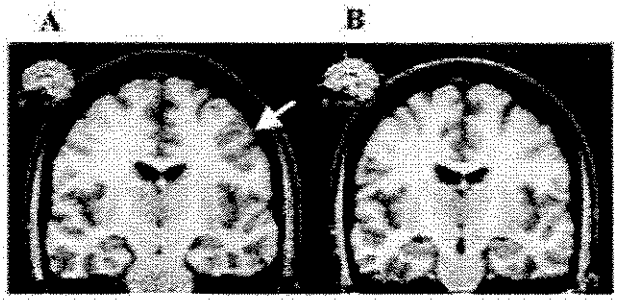


**Fig 2.** Coronal T1-weighted images of a normal subject show the effect of the change in orientation of the planes of section. (A) Area of artifactual cortical thickening (arrow) due to volume averaging. (B) The artifact disappears in a different orientation of the plane of section, as shown by the scout sagittal image in the upper left-hand corner.

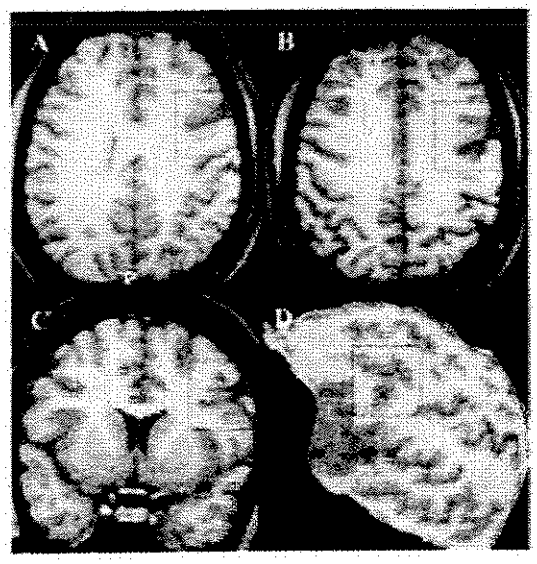

**Fig 3.** Patient 12. T1-weighted images show the same lesion in different planes (boxes). (A, B) Axial images in different planes of section, (C) coronal, and (D) curvilinear reformatting at 16 mm of depth from the cortical surface show the dysplastic lesion in the left frontal lobe (box). Note the cortical thickening, blurring between gray and white matter, and focal atrophy adjacent to the lesion, which can be identified on different planes (A, B, and C), suggesting that the cortical thickening is not the result of an oblique plane of section in relation to the gyrus or volume averaging.

## Discussion

Image-postprocessing techniques, particularly MPR and CR, play an important role in the neuroimaging evaluation of patients with refractory partial epilepsy, especially in the diagnosis of dysplastic lesions. We identified FCD in 12 of 17 selected patients with medically refractory frontal lobe epilepsy without gross structural lesions on MRI. In contrast, the analysis using only plain MRI (as routinely performed) detected the lesion in 6 of these 12 patients.

MPR and CR demonstrated a similar sensitivity in lesion localization. However, the use of CR led to a more precise delineation of the extent of the lesion in 4 of the 12 patients, not only by showing that the cortical dysplasia extended to the normal-appearing areas defined by plain MRI but also by demonstrating that a portion of the area suspected as abnormal was indeed volume averaging in 2 patients. A limitation of CR is the fact that it only provides a contour of the hemispheric convexities, allowing better visualization of lesions localized in the cortical convexity. Therefore, lesions in the mesial frontal, mesial temporal, insular, and orbitofrontal regions are not represented in the CR display.[10] Although the analysis of CR was performed with prior knowledge of the results obtained with plain MRI and MPR, we believe that this approach reflects better the stepwise clinical practice in the investigation of subtle dysplastic lesions; therefore, we feel that CR should be used in addition to the conventional techniques, not in isolation.

It is important to note that although the investigator enrolled in the second step of the project was aware that the 12 selected patients had FCD, and that thin plain MRI included T1 GRE and inversion recovery (sequences both considered ideal for the detection of FCD),[7] he could not identify the lesion on plain MRI in 50% of the patients. However, after a retrospective analysis, subtle but well-characterized features suggestive of FCD could be identified on plain MRI of all patients. Subtle abnor-

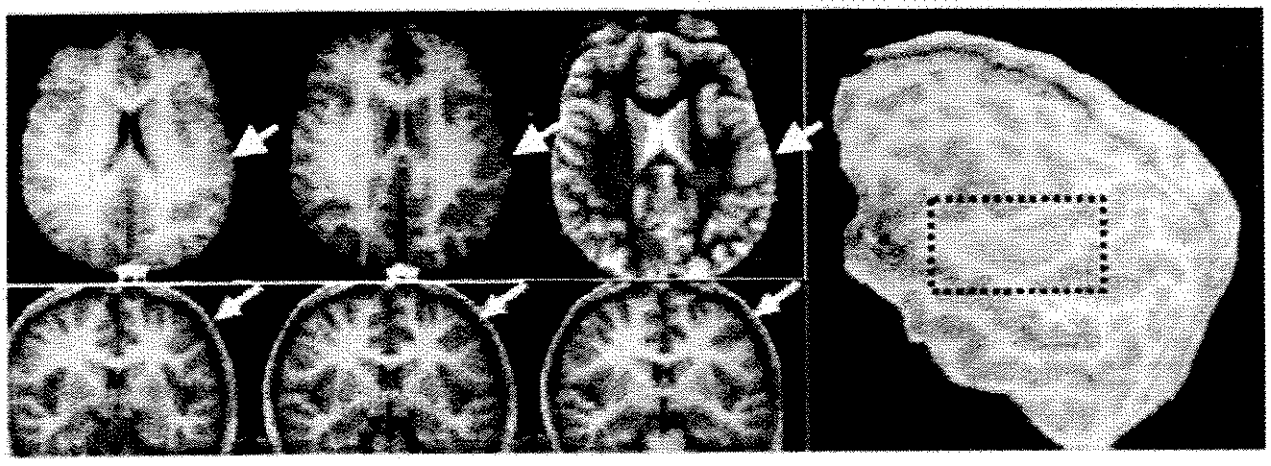

**Fig 4.** Patient 1. Clockwise from upper left-hand corner: axial T1-weighted images show that despite the change in the plane of section, the blurring between the gray and white mater (arrow) does not disappear, indicating that it does not represent volume averaging; axial T2-weighted image shows the hypersignal in the lesion (arrow); curvilinear reformation at 16 mm of depth from the cortical surface shows the dysplastic area in the left postcentral gyrus (box); and sequence of thin (2 mm) coronal T1-weighted images shows the dysplastic area (arrow) in 3 consecutive slices in plane.

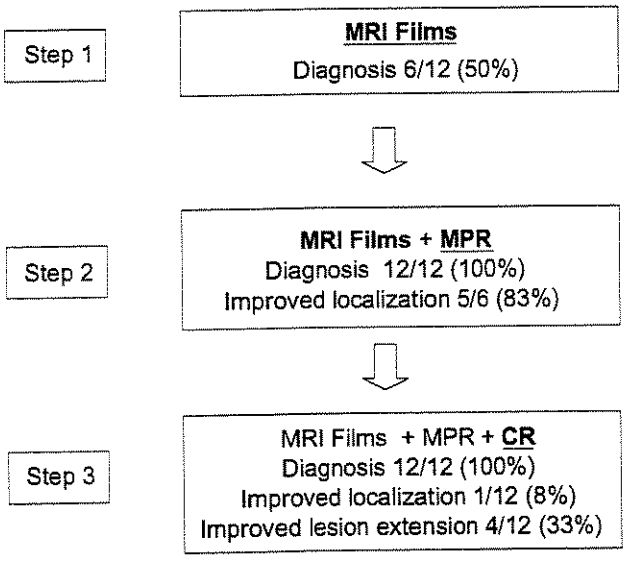


**Fig 5.** Multiplanar reconstruction (MPR) and curvilinear reconstruction (CR): contribution to diagnosis, lesion localization, and extension. MRI = magnetic resonance imaging.

malities associated with focal dysplastic lesions have been described,[11] which assist in the identification of small cortical lesions on high-resolution MRI. This includes an area of cortical thickening on at least 3 sequential slices (thickness = 3 mm) in plane or in both coronal and axial planes associated with at least 1 of the following: (1) a sulcus deeper or straighter than usual, (2) focal tissue loss characterizing a cerebrospinal fluid cleft with cortical dimple,[5,11] or (3) focal hyperintense signal on T2-weighted or FLAIR images. Although these subtle signs may not be sufficient to establish the diagnosis of FCD, these areas should be considered as possibly abnormal and investigated further. We believe that these are the patients in whom MRI postprocessing techniques were most helpful. In patients with FCD already shown by plain MRI, MRI postprocessing can assist in better defining the anatomical location and extent of FCD for surgical planning, as the borders of the lesion shown by plain MRI are usually not well delineated and part of the abnormality may be missed.

Because FCD is usually a subtle lesion, clinical and EEG correlations are mandatory in order to validate the imaging findings. Although 2 of our patients did not present with epileptiform activity in the frontal lobe, they had generalized epileptiform activity, which is frequently seen in patients with frontal lobe epilepsy. Rhythmic interictal epileptiform discharges were recorded in 7 patients. This EEG pattern is frequently associated with dysplastic lesions.[3] All patients had seizure semiology indicating frontal lobe onset (Table 1). It is interesting to note that 1 patient presented eye blinking ipsilateral to the dysplastic lesion. This is one of the few instances in which motor signs can be seen ipsilateral to the epileptic focus.[12]

Although we initially assessed 17 patients with clinical and EEG diagnosis of frontal lobe epilepsy, only 12 had imaging abnormalities compatible with FCD. In 3 of these patients, the lesion was surgically removed, and pathological examination revealed FCD. We understand that pathological verification of all 12 patients would better validate our findings. However, we also believe that the neuroimaging characteristics of FCD are well established and the diagnosis of FCD can be achieved with confidence based only on imaging findings when clinical and EEG findings support this diagnosis.[13]

In this study, we assessed the contribution of MPR and CR to the MRI investigation of FCD; however, this article provides no information about the specificity of these techniques. This is a preliminary finding, and a blinded analysis of a larger sample using both techniques in normal volunteers and other disease states needs to be assessed in order to confirm the results.

We conclude that MPR and CR analysis adds to the neuroimaging evaluation of FCD by improving the lesion diagnosis and localization. CR helps to establish more precisely the extent of the lesion, allowing the visualization of some areas not shown on high-resolution MRI and MPR. These techniques are complementary and do not replace the conventional wisdom of MRI analysis.

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**Patterns of Hippocampal Abnormalities in Malformations of Cortical Development**

**(Submetido)**

# PATTERNS OF HIPPOCAMPAL ABNORMALITIES IN MALFORMATIONS OF CORTICAL DEVELOPMENT

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**Running title**: Hippocampal abnormalities in MCD

**Key words**: malformations of cortical development, hippocampus, volumetric measurements.

**Word count**: title: 9; abstract: 283; text: 1954.

**Number of references:** 29

**Number of figures:** 5

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## ABSTRACT

**Rationale** - Malformations of cortical development (MCD) can be associated with hippocampal abnormalities. Our objective was to assess whether different hippocampal abnormalities are associated with a particular class of MCD.

**Methods** - We evaluated 83 consecutive patients with MRI diagnosis of MCD (37 men, ages ranging from 2 to 58 years; mean=18.5). High resolution MRI was performed in a 2.0T scanner. Volumetric measurements were performed manually on 3mm thick T1-IR coronal slices, perpendicular to the long axis of the hippocampus. Hippocampal volumes were corrected for intracranial volumes and compared to the values of a normal control group of 20 healthy volunteers. Values below or above 2 SD from the mean of the control group were considered abnormal.

**Results** - Twenty-five patients had focal cortical dysplasia, four hemimegalencephaly, five unilateral nodular heterotopia, four bilateral periventricular nodular heterotopia, one transmantle heterotopia, four subcortical laminar heterotopia, five lissencephaly (agyria-pachigyria), five schizencephaly and 30 polymicrogyria. Enlarged hippocampus was present in 44% of patients with MCD due to diffuse migration disorders (2/5 lissencephaly and 2/4 subcortical laminar heterotopia). Conversely, hippocampal atrophy was present in 14% of patients with focal MCD (2/25 focal cortical dysplasia, 3/30 polymicrogyria, 3/5 schizencephaly, 2/5 unilateral nodular heterotopia, and in none with periventricular nodular heterotopia or transmantle heterotopia). Patients with hemimegalencephaly presented both atrophy (n=1/4) or enlargement (n=2/4) of the hippocampus. The hippocampal abnormality

was always ipsilateral to the lesion. Two patients with hippocampal atrophy never presented seizures.

**Conclusion -** We found hippocampal volume abnormalities in 17 (20%) patients with MCD. The pattern of hippocampal abnormality varied according to the type of MCD: enlarged hippocampi in diffuse migration disorders and hippocampal atrophy in focal MCD. Two patients with hippocampal atrophy never presented seizures and the hippocampal abnormality was always ipsilateral to the dysplastic lesion suggesting a common physiopathology for the hippocampal lesion and MCD.

Malformations of cortical development (MCD) are congenital anomalies that may affect different stages of brain development, resulting in various types of cortical abnormalities [1].

There have been reports of hippocampal abnormalities associated with MCD [2-10] however; no special pattern of hippocampal abnormality has been connected to a specific type of dysplastic lesion. Volumetric measurements enabled the identification of subtle hippocampal abnormalities that were usually missed by routine visual inspection [11-12].

The objectives of this study were to assess i) the frequency of hippocampal abnormalities associated with MCD, ii) whether a particular type of hippocampal abnormality (atrophy or enlargement) is associated with the different forms of MCD, and iii) whether hippocampal abnormalities are restricted to particular segments of the hippocampus.

## PATIENTS AND METHODS

We evaluated, prospectively, 83 consecutive patients with MRI diagnosis of MCD, seen at the neurology clinics of our university hospital. All patients were seen and examined by at least one of us. We systematically investigated all patients with any neurological disturbance, even when symptoms were mild, such as speech delay in early childhood.

To classify the MCD we used the neuroimaging system proposed by Barkovich *et al*[1]: a) MCD due to abnormal cellular proliferation/apoptosis (focal cortical dysplasia, hemimegalencephaly); b) MCD due to abnormal neuronal migration (subcortical laminar heterotopia, lissencephaly (agyria-pachigyria), transmantle heterotopia, bilateral periventricular nodular heterotopia, unilateral subcortical heterotopia), and c) MCD due to abnormal cortical organization (polymicrogyria and schizencephaly).

All patients signed an informed consent obtained according to the declaration of Helsinki, and the protocol was approved by the Ethical Committee of our Institution.

MRI was performed in a 2.0 T scanner (Elscint Prestige), using our epilepsy protocol: (*a*) *sagittal* T1 spin-echo, 6mm thick (TR=430, TE=12) for optimal orientation of the subsequent images; (*b*) *coronal* T1 inversion recovery, 3mm thick (flip angle=200°; TR=2800, TE=14, inversion time TI=840, matrix=130X256, FOV=16X18 cm); (*c*) *coronal* T2-weighted "fast spin echo" (FSE), 3-4mm thick, (flip angle= 120°; TR=4800, TE=129, matrix=252X320, FOV=18X18cm), (*d*) *axial* images parallel to the long axis of the hippocampi; T1 gradient echo (GRE), 3mm thick (flip angle=70°, TR=200, TE=5, matrix=180X232, FOV=22X22 cm); (*e*) *axial* T2 FSE, 4mm thick, (tip angle- 120°, TR=6800, TE=129, matrix 252X328, FOV=21X23cm); (*f*) *volumetric (3D)* T1 GRE, acquired in the sagittal plane for multiplanar reconstruction (MPR), 1 - 1.5mm thick (TA=35°, TR=22, TE=9, matrix=256X220, FOV=23X25cm).

Volumetric measurements were performed on 3mm thick coronal T1-IR images using an interactive, semiautomatic software program developed by NIH (NIH-image). The regions of interest were outlined using a manual contouring editing function. Once the

outline had been defined, the slice volume was calculated automatically by the computer program. The individual variance of the hippocampal volume was corrected using the following formula:

$$\text{Corrected HV} = \frac{\text{MBV}}{\text{IBV}} \times \text{HV}$$

Where: MBV is the mean brain volume in the control group (which is a constant), HV is the individual hippocampal volume, and IBV is the individual brain volume.

Hippocampal volumes of each patient were obtained and compared with the values from a normal control group of 20 healthy volunteers. Values < or > 2 standard deviations (SD) from the mean of the control group were considered abnormal.

We analyzed the occurrence of hippocampal abnormality according to each group of MCD: a) abnormal cellular proliferation/apoptosis, b) abnormal neuronal migration, and c) abnormal cortical organization.

Moreover, in order to assess the profile of the hippocampal abnormality, the mean hippocampal volume of each hippocampal slice was plotted in a graphic with the mean volume, and the SD, of the correspondent hippocampal slice of the control group. The individual variance of each slice was corrected according to the intracranial volume of

each patient. The analysis of the graphics was divided into two parts: individual patients and each type of MCD, as a group.

We used the chi-square and Fischer exact test to examine differences in the proportion of hippocampal volume abnormalities in each group of MCD.

## RESULTS

There was 37 men and 46 women with ages ranging from 2 to 58 years (mean=18.5). Twenty-five patients had focal cortical dysplasia, four hemimegalencephaly, five lissencephaly (agyria-pachigyria), four subcortical laminar heterotopia, five unilateral nodular heterotopia, four bilateral periventricular nodular heterotopia, one transmantle heterotopia, five schizencephaly and 30 polymicrogyria.

Hippocampal atrophy (figure 1) was present in 2/25 patients with focal cortical dysplasia, 1/4 of hemimegalencephaly, 2/5 of unilateral nodular heterotopia, 3/5 of schizencephaly, and 3/30 of polymicrogyria. Although hippocampal atrophy was present in all three groups of MCD, it occurred only in patients with focal MCD.

Conversely, an enlarged hippocampal (figure 2) was present only in patients with MCD due to diffuse abnormal migration (lissencephaly, subcortical laminar heterotopia): 2/5 of patients with lissencephaly (agyria-pachigyria), 2/4 of subcortical laminar heterotopia and 2/4 of hemimegalencephaly. Table 1 shows the characteristics of the patients with hippocampal abnormalities. Abnormalities in the internal structure of the hippocampus were present in 6 patients and hyperintense signal on T2 or FLAIR images in

3 (table 2). Table 3 shows the analysis of the hippocampal abnormality according to each group of MCD.

Overall, the frequency of hippocampal abnormalities in patients with MCD was 20%. It occurred in 14% of patients with focal MCD and in 44% of patients with diffuse MCD.

When the volume of each hippocampal slice was plotted in a graphic, we found that patients with lissencephaly (agyria-pachigyria) and subcortical laminar heterotopia not only had an enlarged, but also a shorter hippocampus (figure 3).

The analysis of the graphics showed that, individually, the hippocampal abnormality could be more severe in a particular segment of the hippocampus; however, we did not identify any specific pattern of predominance in any type of MCD.

Sixty-four patients (77%) presented epilepsy. All patients with abnormally enlarged hippocampus had epilepsy. Among the 11 patients with hippocampal atrophy, nine had epilepsy and two never presented seizures (table 1). Only one patient presented febrile seizure during childhood. This patient has focal cortical dysplasia, and normal hippocampal volume.

## DISCUSSION

Volumetric measurements of hippocampal formation is an important research tool because it provides numerical data that can be compared to other variables and validated by statistics, including the degree of post-operative pathological abnormalities [11-13].

Dual pathology has been defined by hippocampal atrophy associated with an extra-hippocampal lesion. The most common type of extra-hippocampal lesion found in dual pathology has been MCD [5, 6, 9, 14]. MCD was found to be associated with hippocampal atrophy in 25% of the patients and in patients with epilepsy, both the atrophic hippocampus as well as the extra-hippocampal lesions are likely to be involved in seizure generation [5, 6, 8, 14]. This brought a new perspective in the neuroimaging evaluation of patients with MCD, since one should consider as surgical target not only the focal cortical lesion, but also the temporal mesial structures whenever possible [6]. In these patients a more extensive EEG and neuroimaging investigation should be considered.
In this study, hippocampal atrophy was present in 14% of patients with focal MCD. The etiology of hippocampal atrophy has not been established yet. Complex febrile seizures, *status epilepticus* and genetic predisposition are most likely etiological factors [15-20].

The issue of prolonged febrile seizures early in life leading to hippocampal atrophy and temporal lobe epilepsy still remains controversial. A subtle pre-existing hippocampal malformation may facilitate febrile convulsions and contribute to the development of subsequent hippocampal atrophy [21]. However, only one of our patients studied here presented febrile seizure during childhood. She has a focal cortical dysplasia in the frontal lobe, and normal hippocampal volume.

*Status epilepticus* is a well documented cause of hippocampal atrophy, however it is still unclear if habitual brief partial seizures can cause progressive hippocampal atrophy in patients with intractable temporal lobe epilepsy, or if they play a role in the progression of hippocampal pathology [15-17, 22]. In rat pups with MCD produced by the *in utero*

exposure of methylazoxymethanol acetate (MAM), seizures produce a lowered after discharge threshold and more rapid hippocampal kindling [23]. Multiple seizures or *status epilepticus* may explain the occurrence of hippocampal atrophy in some patients, however, the more recent findings of hippocampal atrophy in individuals who had only a few seizures in life is a strong indicator that partial seizures alone may not be sufficient to induce hippocampal atrophy [15, 17, 24, 25].

A vascular injury is likely to be involved in the pathogenesis of some forms of MCD [26, 27]. Unilateral periventricular nodular heterotopia usually involves watershed areas in the frontal and occipital-temporal regions, and sometimes these lesions are associated with hippocampal atrophy in the same side of the heterotopia (figure 1). This raises the possibility that, in such patients, both lesions are caused by vascular injury in early development [9].

Moreover, the finding of a necrotic cortical layer in patients with polymicrogyria supports the traditional theory that these abnormalities represent a form of destructive lesion, probably due to an early vascular injury [26, 27]. Since two of our patients with bilateral focal polymicrogyria (perisylvian syndrome) and hippocampal atrophy never had seizures, we may suggest that a vascular injury (or other type of pre-natal injury) may have caused both the hippocampal atrophy and focal MCD.

A proportionally enlarged hippocampus was present in 44% of patients with MDC due to diffuse abnormal neuronal migration. The hippocampal enlargement was bilateral in these patients. The pathogenesis of the abnormally enlarged hippocampi is still unclear. Modified cell death has been proposed as having a role in the genesis of MCD due to

abnormal cellular proliferation/apoptosis and neuronal migration [1, 28]. One may speculate that the hippocampal enlargement and the diffuse dysplastic lesion (lissencephaly and subcortical laminar) share the same pathogenesis. In this case, abnormal programmed cell death would result in an excess of neurons, and consequently an enlarged hippocampus. Unfortunately, we were not able to assess the pathology of these abnormally enlarged hippocampi.

It is interesting to note that although the hippocampus can be proportionally enlarged in patients with diffuse MCD, it can be missed by visual inspection because the temporal horn of the lateral ventricles are usually also enlarged, giving the appearance of a small hippocampus [29].

We could not establish a constant pattern of abnormality affecting a particular hippocampal segment. That is probably because the hippocampal abnormality predominated according to the region of the brain where the MCD was more severe: anterior or posterior. This is a preliminary finding, and a larger sample is needed to confirm these results. The visual analysis of the MRI characteristics of the hippocampal abnormality showed the atrophy present in our patients did not always correlate with the findings commonly seen in patients with classic hippocampal sclerosis. We found abnormalities in the internal structure of the hippocampal in only 5/11 patients with hippocampal atrophy, and hyperintense signal on T2 or FLAIR images in only 2. Moreover, it is interesting to note that all but one patient (patient 3, presenting hemimegalencephaly) with enlarged hippocampi had normal internal structure and signal.

Regarding the hippocampal shape and rotation, either atrophic or enlarged hippocampus presented abnormalities (table 2, figure 4).

It should be clarified that hemimegalencephaly was associated with either small or enlarged hippocampus. It can be explained by the fact that this MCD results from abnormalities during all three fundamental stages of cortical development: cellular proliferation/apoptosis, neuronal migration and cortical organization [1]. When abnormalities of proliferation/apoptosis or migration predominated in the temporal lobe, the hippocampus was enlarged (figure 5). Conversely, when cortical organization abnormalities predominated in the temporal lobe, we found a small hippocampus.

We conclude that developmental abnormalities of the hippocampus are frequently present in patients with MCD (20%). Hippocampal atrophy is associated with focal MCD (polymicrogyria, schizencephaly, focal cortical dysplasia, unilateral nodular heterotopia and hemimegalencephaly). Abnormally enlarged hippocampus is associated to diffuse MCD due to abnormal neuronal migration (lissencephaly and subcortical laminar heterotopia). The hippocampal abnormality was always ipsilateral to the dysplastic lesion suggesting a common physiopathology for both the hippocampal lesion and MCD.

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