LUIZ EDUARDO GOMES GARCIA BETTING

EPILEPSIA GENERALIZADA IDIOPÁTICA:
aspectos clínicos, eletroencefalográficos e de neuroimagem

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A minha amada esposa Tálita,
por sua fundamental ajuda.

Aos meus irmãos
Carlos, Paulo e Marcos.

Aos meus pais
Luiz Carlos e Ruth.

A meu mentor e orientador professor doutor Fernando Cendes pela confiança e apóio.

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A todos aqueles que comigo conviveram nos últimos anos e participaram deste trabalho.

Aos pacientes e seus familiares.

O paciente com epilepsia
deve passar o dia acordado e a noite dormindo.
Se este hábito for perturbado,
não é bom... pior ainda se o paciente
não dormir nem durante o dia e nem durante a noite

Hipócrates

CSC	Concentração de substância cinzenta
CTCG	Crises tônico-clônicas generalizadas
EA	Epilepsia ausência
EAI	Epilepsia ausência infantil
EAJ	Epilepsia ausência juvenil
EEG	Eletroencefalograma
EGI	Epilepsia generalizada idiopática
EMJ	Epilepsia mioclônica juvenil
GABA	Ácido gama-aminobutírico
MBV	Morfometria baseada em voxel
RM	Ressonância magnética

RESUMO

Epilepsias generalizadas idiopáticas (EGI) constituem de 20-40% das epilepsias e de forma oposta às epilepsias parciais, anormalidades estruturais não são esperadas. De acordo com a idade de início e o tipo principal de crise, as EGI são divididas principalmente em epilepsia ausência infantil e juvenil (EA), epilepsia mioclônica juvenil (EMJ) e epilepsia com crises tônico-clônicas generalizadas (CTCG). Os limites entre estas subsíndromes são imprecisos e a classificação muitas vezes é difícil. Devido às características semelhantes, alguns autores consideram a EGI como uma única patologia com múltiplos fenótipos (continuum biológico).

O eletroencefalograma (EEG) auxilia no diagnóstico das EGI especialmente quando evidencia descargas do tipo espícula onda-lenta generalizadas com atividade de base normal. Entretanto, o EEG pode ser normal e até mesmo mostrar focalidades dificultando o diagnóstico.

A ressonância magnética (RM) não é realizada de forma rotineira em pacientes com EGI. Contudo, novas técnicas de aquisição e processamento de imagens vêm detectando anormalidades sutis nestes indivíduos.

O objetivo deste estudo foi investigar a fisiopatologia das EGI através da análise de características clínicas, eletroencefalográficas e de neuroimagem.

Inicialmente, as características dos EEGs de 180 pacientes com diagnóstico clínico de EGI foram avaliadas. 493 exames foram analisados. Em 33% dos pacientes o EEG inicial foi característico e em 22% o exame evidenciou focalidades.

Após a identificação de focalidades utilizamos a neuroimagem convencional (análise visual) na avaliação de 134 pacientes com EGI. Observamos anormalidades na RM de 27 (20%) pacientes. A maioria das anormalidades não apresentou relação direta com as crises.

Utilizamos a técnica da morfometria baseada em voxel (MBV) para investigar lesões discretas eventualmente não identificadas na neuroimagem de rotina. Esta técnica permite a comparação entre grupos de imagens aumentando a chance de detecção de anormalidades.

Observamos aumento na concentração de substância cinzenta (CSC) localizada no córtex frontal de pacientes com EMJ (n=44) e EA (n=24). Observamos também uma maior CSC na região anterior do tálamo nos pacientes com crises de ausência (n=47). Avaliando as focalidades clínicas e de EEG de 22 pacientes com EGI utilizando a MBV, observamos áreas de aumento da CSC em 8 dos 9 (89%) pacientes com EMJ, 5 dos 6 (83%) pacientes com EA e 5 dos 7 (71%) pacientes com CTCG ao despertar. A volumetria do tálamo foi realizada para investigar o aumento de CSC sugerido pela MBV. A comparação entre 147 pacientes e um grupo controle evidenciou um maior volume da região anterior do tálamo nos pacientes com crises de ausência.

Nossos resultados revelam que a fisiopatologia das EGI envolve o tálamo e o córtex cerebral. As diversas alterações na neuroimagem quantitativa apresentadas por cada subsíndrome sugerem um diferente mecanismo para as EGI. Este achado fortalece o conceito de diferentes doenças com fenótipos semelhantes. Mais do que isso, nossos achados indicam, uma alteração estrutural no cérebro destes indivíduos. Os diversos fenótipos estão relacionados a diferentes mecanismos fisiopatológicos. As focalidades observadas no EEG e na RM refletem a patogênese das crises em pacientes com EGI.

ABSTRACT

Idiopathic generalized epilepsies (IGE) represent 20-40% of all epilepsies and opposed to partial epilepsies, structural abnormalities are not expected. According to the age of onset and the main seizure type, IGE are divided mainly in childhood and juvenile absence epilepsy (AE), juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures (GTCS). The limits between these subsyndromes are unclear and sometimes classification is difficult. Because of the similar characteristics, some authors consider IGE as a single pathology with multiple phenotypes (biological continuum).

Electroencephalogram (EEG) helps the IGE diagnosis specially when it shows the generalized spike and wave discharges with normal background. However, the EEG may be normal or even disclose focalities difficulting the diagnosis.

Magnetic resonance imaging (MRI) is not routinely performed in patients with IGE. In spite of this, new techniques of acquisition and processing of the images are detecting subtle abnormalities in these individuals.

The objective of this study was to investigate the pathophysiology of the IGE using the clinical, EEG and neuroimaging features.

Initially, the characteristics of the EEGs of 180 patients with clinical diagnosis of IGE were evaluated. 493 exams were analyzed. In 33% of the patients the initial EEG was characteristic and in 22% the exam revealed focalities.

After the identification of the focalities, we used conventional neuroimaging (visual analysis) on the evaluation of 134 patients with IGE. We observed abnormalities in the MRI of 27 (20%) patients. Most of the abnormalities were not directly related to the seizures.

We used the voxel base morphometry (VBM) technique to evaluate the images. This technique allows comparisons between groups of images increasing the chances of detecting abnormalities. We observed increased gray matter concentration (GMC) localized in the frontal cortex of patients with JME (n=44) and AE (n=24). We also observed increased GMC in the anterior thalamic region of patients with absence seizures (n=47).

Evaluating the clinical and EEG focalities of 22 patients with IGE using VBM, we observed areas of increased GMC in 8 of 9 (89%) patients with JME, 5 of 6 (83%) patients with AE and 5 of 7 (71%) patients with GTCS on awakening. The volumetry of the thalamus was performed to investigate the increased GMC suggested by the VBM. The comparison between 147 patients with a control group showed increased volume of the anterior thalamic region in patients with absence seizures.

Our results revealed that the pathophysiology of the IGE involves the thalamus and the cerebral cortex. The several abnormalities on the neuroimage presented by each subsyndrome suggest a different mechanism for the IGE. This finding strengths the concept of multiple diseases with similar phenotypes. Furthermore, our findings indicate a structural abnormality in the brain of these individuals. The several phenotypes are related with different pathophysiological mechanisms. The focalities present on the EEG and in the MRI reflect the pathogenesis of the seizures in patients with IGE.

1- INTRODUÇÃO E REVISÃO DA LITERATURA

Quadro clínico

As epilepsias generalizadas idiopáticas (EGI) são um grupo de síndromes bastante freqüentes correspondendo a um terço de todas as epilepsias [PANAYIOTOPOULOS, 2002]. Segundo critérios da Liga Internacional Contra Epilepsia, as EGI são caracterizadas pelo início das crises relacionado à idade [COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY - ILAE, 1989]. Os três tipos de crises generalizadas podem estar presentes.

Crises de ausência

Clinicamente caracterizam-se por perda súbita de consciência com duração de segundos. Durante as crises podem existir automatismos orais discretos e piscamento palpebral. Sua duração é menor do que 30 segundos. Em indivíduos sem tratamento são facilmente desencadeadas pela hiperventilação.

Crises mioclônicas

São crises de curta duração geralmente sem o comprometimento da consciência. Durante a crise ocorrem abalos rápidos, súbitos, irregulares predominantes nos membros superiores. Quando as crises ocorrem de forma repetitiva podem levar o indivíduo à queda. De forma semelhante às ausências, estas crises dificilmente levam o paciente a procurar o auxílio médico. Desta forma, para o diagnóstico adequado, é necessário questionar o paciente de forma direta e objetiva sobre a presença destas crises.

Crises tônico-clônicas generalizadas (CTCG)

É a crise que leva o paciente a procurar auxílio médico devido à sua apresentação clínica exuberante. Na fase inicial, o paciente perde a consciência e apresenta contração tônica de toda musculatura. A contração diafragmática pode levar a emissão de um som semelhante a um grito. Em seguida, a fase tônica se encerra dando lugar a abalos

clônicos dos membros. No período pós-ictal, o paciente encontra-se exausto, geralmente ocorre sonolência e confusão mental. Lesões da mucosa oral podem estar presentes após a crise.

Classificação sindrômica

De acordo com a idade de início e o tipo predominante de crise, as EGI são divididas em subsíndromes. As principais subsíndromes que acometem adolescentes e adultos são:

- **Epilepsia ausência da infância (EAI):** corresponde a 2-10% das crianças com epilepsia. Idade de início com pico entre os 5-6 anos. As crises de ausência típica predominam de forma nítida. As crises são extremamente freqüentes podendo ocorrer centenas por dia (ausências picnolépticas). Alguns autores acreditam que a forma pura de EAI é autolimitada não chegando até a idade adulta. Fotossensibilidade, início precoce de CTCG e refratariedade ao tratamento clínico indicam um mau prognóstico para o controle das crises [PANAYIOTOPOULOS, 1997, 2002]. O EEG auxilia muito o diagnóstico evidenciando complexos espícula onda lenta generalizados com 3Hz e atividade de base normal.
- **Epilepsia ausência juvenil (EAJ):** corresponde a 8-10% das EGI [PANAYIOTOPOULOS, 1997, 2002]. Idade de início de 9-13 anos. Também predominam as crises de ausência porem são menos freqüentes que na EAI (ausências espaniolépticas). As CTCG são inevitáveis ocorrendo em até 80% dos pacientes. Sua duração provavelmente é por toda vida.
- **Epilepsia mioclônica juvenil (EMJ):** forma mais freqüente de EGI correspondendo a 26% das EGI e 5-10% de todas as epilepsias [JANZ e DURNER, 1997]. Idade de início por volta de 14-15 anos. Geralmente as crises iniciam quando o indivíduo é submetido a algum fator precipitante como privação de sono ou uso de bebidas alcoólicas. As mioclonias predominam, ocorrendo principalmente pela manhã. CTCG são freqüentes incidindo em quase todos os pacientes especialmente após crises mioclônicas.

- **Epilepsia com CTCG apenas:** corresponde a 13-15% das EGI. A idade de início tem pico entre os 16-17 anos, porém, pode variar de 6 até 47 anos. O tipo predominante de crise é a CTCG. De acordo com a relação com o ciclo sono-vigília esta subsíndrome é dividida em [WOLF, 1992; ANDERMANN e BERKOVIC, 2001; PANAYIOTOPOULOS, 2002]:

  • CTCG ao despertar (17-53%): as crises ocorrem geralmente 30 minutos após o despertar. Entretanto, estas podem ocorrer também a tarde em um período de relaxamento. Em pacientes que apresentam epilepsia de longa duração, sobretudo com tratamento inadequado, as crises podem perder a relação com o despertar dificultando o diagnóstico;

  • CTCG difusas durante a vigília (23-36%);

  • CTCG durante o sono (27-44%);

  • CTCG randômicas (13-26%).

- **Epilepsia generalizada idiopática com início no adulto:** previamente considerada rara. Não pertence à atual classificação da ILAE. Indivíduos com crises generalizadas de início após os 30 anos, EEGs generalizados e história familiar positiva para epilepsia são candidatos a este diagnóstico [CUTTING et al., 2001; MARINI et al., 2003].

A literatura permanece controversa a respeito da presença de múltiplas subsíndromes de EGI ou apenas uma doença conhecida como EGI e diversos espectros clínicos. Mais do que isso, certos tipos de epilepsia de lobo frontal têm características clínicas muito semelhantes às EGI. Alguns autores sugerem que alguns tipos de epilepsia de lobo frontal e as subsíndromes de EGI pertencem a um mesmo *continuum biológico* sendo as formas mais clássicas os extremos [BERKOVIC et al., 1987; PANAYIOTOPOULOS, 1997].

Eletroencefalograma

A assinatura neurofisiológica da EGI é caracterizada pelos complexos espícula ou poliespícula onda lenta generalizados com atividade de base normal. Os complexos podem ser regulares como na EAI ou ocorrerem de forma irregular como na EMJ.

Apesar de ser um marcador das EGI, o EEG pode ser normal neste grupo de pacientes. De acordo com WALTZ (2000), não há um marcador eletroencefalográfico interictal específico para o diagnóstico das EGI e, sobretudo EMJ. O diagnóstico de uma subsíndrome deve ser baseado na avaliação clínica cuidadosa. A chance de detecção de anormalidades características é aumentada com a utilização de métodos de ativação (fotoestimulação e hiperventilação), privação de sono, exames seriados e exames próximos ao período ictal.

A fotoestimulação é um método de ativação bastante utilizado em eletroencefalografia. A fotossensibilidade é transmitida geneticamente. Dentre as EGI a EMJ parece ser a subsíndrome mais relacionada com fotossensibilidade. Este achado é encontrado em 20-57% dos pacientes com EMJ [WALTZ, 2000].

As ausências são facilmente estudadas através do EEG. Praticamente todos os pacientes com este tipo de crise apresentaram descargas generalizadas durante a hiperventilação [PANAYIOTOPOULOS, 1997, 2002]. Para pacientes com EMJ e CTCG a hiperventilação não é tão eficaz como nas ausências.

Em pacientes com EGI de início tardio o EEG com freqüência é persistentemente normal. O uso de medicação, sobretudo o valproato, e a longa duração da epilepsia estão relacionados com a mudança no padrão encontrado no EEG [YENJUN et al., 2003].

Apesar das descargas generalizadas serem as marcadoras das epilepsias generalizadas, atividade focal pode ser evidenciada em 8-55% dos casos em EMJ [WALTZ, 2000]. Por vezes, as focalidades sugerem bissincronia secundaria ou epilepsia parcial levando a um atraso no diagnóstico das EGI. Na EAI, o EEG interictal pode evidenciar descargas epileptiformes na região centro-temporal e occipital.

Outro padrão associado a EAI é caracterizado por atividade delta rítmica posterior. O padrão da EAJ é semelhante a EAI. Focalidades e fragmentação das descargas podem estar presentes [PANAYIOTOPOULOS, 1997]. Nos pacientes com CTCG, o EEG difere de acordo com a distribuição das crises. Pacientes com CTCG ao despertar apresentam uma maior porcentagem de anormalidades generalizadas quando comparados com pacientes com CTCG durante o sono. Além disso, focalidades são raramente encontradas (2.6%) [JANZ, 2000].

Diversas hipóteses foram feitas na tentativa de explicar os mecanismos destas focalidades. Acredita-se que as descargas localizadas podem representar descargas generalizadas fragmentadas. As focalidades podem também representar áreas de hiperexcitabilidade cortical que se perpetuam. Outra possibilidade seria a existência de áreas anormais no córtex cerebral, por exemplo, pequenas áreas de displasia. Entretanto, a fisiopatologia por traz das focalidades no EEG de pacientes com EGI permanece em estudo [LOMBROSO, 1997; LEUTMEZER et al., 2002].

Neuroimagem

O estudo por imagem de pacientes com EGI é de longa data. Em 1969 KAMMERER avaliando radiografias descreveu um adelgaçamento do osso frontal em pacientes com EGI. Entretanto, este estudo apresentava falhas metodológicas como a ausência de critério para medir a espessura do osso bem como diferentes formas de radiografia.

Em 1984, MEENCKE e JANZ realizaram um estudo anatomo-patológico de 8 pacientes com EGI. Estes autores observaram anormalidades estruturais corticais compatíveis com microdisgenesias. O achado foi bastante discutido. Porém, esta descrição deu suporte para a procura por anormalidades estruturais sutis em pacientes com EGI.

A descrição de pacientes com heterotopias ventriculares e quadro clínico semelhante as EGI, reforçou a hipótese de que pelo menos parte deste grupo de epilepsias poderiam ser secundarias a lesões estruturais [RAYMOND, et al., 1994; DUBEAU et al., 1995; FISH et al., 1995].

De acordo com JANZ (1989), a investigação através da tomografia computadorizada e ressonância magnética (RM) não revelou nenhuma alteração relevante em uma série de pacientes com EMJ. Entretanto, este autor relatou sinais freqüentes de atrofia cortical difusa nestes pacientes.

GELISSE et al. (2000) avaliaram 82 pacientes com EMJ (22 com RM), 13 (16%) apresentaram anormalidades estruturais. No entanto, as anormalidades não estavam diretamente relacionadas com as crises. A RM anormal não influenciou nas decisões terapêuticas nem no prognóstico destes pacientes.

Em outro estudo investigando o uso clínico da neuroimagem em epilepsia, WIESHMANN (2003) avaliou 31 pacientes com EGI. 14 pacientes foram submetidos a RM e apenas um a RM de alta resolução com cortes de 1,5 milímetros. O autor encontrou anormalidades em apenas um paciente. A anormalidade descrita foi uma lesão única e pequena na substância branca do tronco cerebral.

Com o desenvolvimento de novas técnicas de imagem, as descrições de anormalidades no cérebro de pacientes com EGI aumentaram.

RM estrutural

WOERMANN et al. (1998), utilizando uma técnica de segmentação semi-automática demonstraram uma maior concentração total de substância cinzenta nos cérebros de pacientes com EGI. Foram avaliados 20 pacientes com EMJ, 10 pacientes com EAI e 10 com EAJ e 5 pacientes com CTCG ao despertar. Todos os grupos individualmente comparados com 30 controles mostraram aumento difuso da concentração de substância cinzenta (CSC).

Em uma avaliação da RM de 10 pacientes com CTCG primárias, utilizando um programa que permitiu a comparação de tamanho, proporção intrínseca e formato do cérebro, SAVIC et al. (1998) demonstraram que estes pacientes apresentavam um achatamento do cérebro na direção crânio-caudal em comparação com 20 indivíduos controles. A porção anterior do cérebro também se apresentou relativamente alongada quando comparada com a posterior. Estas alterações não foram observadas em pacientes com crises parciais ou secundariamente generalizadas.

Utilizando a morfometria baseada em voxel (MBV), WOERMANN et al. (1999) estudaram 20 pacientes com EMJ. Em comparação com um grupo de 30 controles, os autores encontraram uma maior CSC localizada nas regiões frontais mesiais. Na comparação individual entre cada paciente e os controles, 5 dos 20 pacientes apresentaram áreas de alteração na CSC. Dois apresentaram áreas de aumento e três áreas de diminuição da CSC.

NATSUME et al. (2003) realizaram uma análise volumétrica do tálamo em 17 pacientes com EGI. As características clínicas não foram fornecidas. Neste estudo não houve diferença no volume dos pacientes em comparação com controles. Em outro estudo deste mesmo centro, o volume talâmico de 20 pacientes com EGI não diferiu quando comparado com 21 controles [BERNASCONI et al., 2003]. Dos 20 pacientes estudados, 9 apresentavam controle insatisfatório das crises.

Os volumes de estruturas subcorticais incluindo o núcleo caudado, putamem, globo pálido e o tálamo foram determinados em 11 pacientes com EGI e comparados com 15 controles por SEECK et al. (2005). Os autores observaram um menor volume do putamem nos pacientes com EGI. Entre as subsíndromes estudadas, 5 pacientes foram classificados como EMJ, 4 EAJ e 2 CTCG ao despertar.

Neuroimagem funcional

- **Espectroscopia:** A espectroscopia por RM é um método bastante utilizado na avaliação das EGI. Existem evidências de alterações metabólicas no tálamo e na região frontal dos pacientes com EGI. Estas alterações sugerem anormalidades funcionais nestas regiões [BERNASCONI et al., 2003; MORY et al., 2003; SIMISTER et al., 2003]. Avaliando 26 pacientes com EMJ e 20 com CTCG, SAVIC et al. (2004) demonstraram redução do N-acetil-aspartato na região frontal apenas dos pacientes com EMJ. Por outro lado, os dois grupos apresentaram uma alteração talâmica quando comparados com controles. Este estudo sugere uma diferente fisiopatologia para estas subsíndromes.
- **RM funcional:** Em um estudo de 15 pacientes com EGI utilizando uma técnica que combina RM funcional e EEG, AGHAKHANI et al. (2004) demonstraram que 14 (93%) apresentaram alterações corticais. As alterações observadas foram ativação e desativação.

O achado ocorreu de forma simétrica nos dois hemisférios cerebrais envolvendo as regiões anteriores e posteriores. Alterações talâmicas bilaterais também foram evidenciadas em 12 pacientes (80%). A ativação predominou no tálamo e o oposto ocorreu com o córtex cerebral.

- **Tomografia por emissão de positrons:** Avaliando o metabolismo e consumo de oxigênio do tálamo, PREVETT et al. (1995) conseguiram demonstrar pela primeira vez um fluxo sanguíneo mais elevado nesta estrutura durante as crises de ausência.

Na avaliação de receptores, KOEPP et al. (1997) mostraram um acúmulo de radioisótopos localizado no tálamo, córtex e cerebelo indicando uma maior concentração de receptores benzodiazepínicos/ácido gama-aminobutírico A ($GABA_A$). O achado deste estudo sugeriu uma maior densidade neuronal nestas regiões.

Fisiopatologia

Ausências

O modelo inicial da fisiopatologia para crises de ausência proposto em 1954 por PENFIELD e JASPER, foi baseado na anormalidade eletroencefalográfica. A teoria centrencefálica sugeria que uma atividade anormal proveniente de estruturas cerebrais profundas recrutaria ambos hemisférios cerebrais levando então as crises. Entretanto, evidências apontavam também para a importante participação do córtex cerebral na gênese das descargas generalizadas [GIBBS e GIBBS, 1952; BENNETT, 1953].

Em 1969, GLOOR na tentativa de conciliar os modelos anteriores formulou a hipótese de que a interação do tálamo com o córtex hiperexcitável seria um ponto chave na fisiopatologia das ausências e das EGI. Segundo esta teoria, oscilações geradas no núcleo reticular do tálamo seriam posteriormente transformadas em descargas generalizadas pelo córtex cerebral hiperexcitável.

Portanto, as evidências experimentais apontam para o tálamo e para o córtex como protagonistas principais na patogênese das descargas generalizadas presentes nas EGI. Alguns estudos ressaltam o tálamo como estrutura principal na gênese das descargas

generalizadas [BUZSÁKI, 1991]. Outros autores ressaltam que as EGI seriam a expressão de uma anormalidade cortical [NIEDERMEYER, 1996]. MEEREN et al (2002), através do estudo experimental de crises de ausência, observaram que as descargas generalizadas iniciavam na região perioral do córtex somatosensitivo. Desta região, a crise generalizava rapidamente por todo o córtex. O tálamo inicialmente é conduzido pelo córtex. Posteriormente a interação entre estas estruturas é fundamental para a amplificação e manutenção das descargas. De forma semelhante à hipótese cortico-reticular proposta por GLOOR em 1969, esta teoria - denominada teoria do foco cortical - tenta conciliar as duas estruturas principais envolvidas na fisiopatologia das EGI.

Mecanismo das crises de ausência

O mecanismo envolvido nas crises de ausência e de forma geral responsável pelas descargas generalizadas nas EGI envolve três populações neuronais principais. Os neurônios reticulares do tálamo, neurônios de relé do tálamo e os neurônios piramidais corticais. Os neurônios de relé podem ativar os neurônios corticais de forma tônica ou fásica. A ativação de forma tônica ocorre durante a vigília e no sono REM. A ativação de forma fásica ocorre no sono não-REM. O modo de ativação do córtex (tônico ou fásico) é controlado por impulsos dos neurônios reticulares que podem hiperpolarizar os neurônios relés permitindo que eles disparem de forma fásica. Os neurônios reticulares podem ser inibidos por eles mesmos. Os neurônios corticais e os neurônios de relé projetam para os neurônios reticulares fechando assim o circuito. Impulsos ascendentes noradrenérgicos, serotoninérgicos e dopaminérgicos modulam este circuito alterando a probabilidade da ativação do córtex de forma fásica. No sono não-REM normal, o córtex é ativado de forma fásica criando os elementos neurofisiológicos observados regularmente. Durante a vigília, os neurônios de relé ativam o córtex de forma tônica permitindo a transferência de impulsos sensoriais de forma arrítmica. Uma falha neste circuito ativará o córtex de forma fásica durante a vigília provocando desta forma as descargas rítmicas observadas no EEG durante a crise de ausência [CHANG e LOWENSTEIN, 2003].

Mioclonias

As mioclonias apresentam diversos mecanismos fisiopatológicos. De forma geral, com exceção das mioclonias espinhais, estas são ocasionadas por uma descarga altamente sincronizada que é transmitida até os neurônios motores pelas vias descendentes. Finalmente, os neurônios motores são ativados gerando a contração de grupos musculares. As mioclonias podem ser desencadeadas por diversas anormalidades em distintas regiões do sistema nervoso.

As mioclonias presentes nas EGI são provavelmente ocasionadas por descargas corticais altamente sincronizadas. O sistema tálamo-cortical de forma semelhante às ausências seria responsável pela manutenção das descargas [AVANZINI et al., 2000].

Crises tônico-clônicas generalizadas

Duas regiões cerebrais estão envolvidas no mecanismo fisiopatológico das CTCG: o córtex, sobretudo o lobo frontal, e o tronco cerebral. De acordo com modelos animais, estes circuitos apresentam um funcionamento distinto e a estimulação de ambos pode levar as CTCG. Sob condições especiais como lesões estruturais e crises freqüentes, estes circuitos podem interagir. As CTCG clássicas presentes em pacientes com EGI provavelmente relacionam-se a descargas anômalas provenientes do tronco cerebral [BROWNING, 1994].

Tratamento

Medidas gerais

As orientações para os pacientes com EGI podem ser tão importantes quanto o tratamento medicamentoso. Estas orientações devem envolver a relação das crises com o ritmo circadiano, estilo de vida e fatores desencadeantes das crises. O controle apropriado das crises será alcançado com sucesso apenas se houver uma boa aderência ao tratamento medicamentoso e se o paciente evitar de forma adequada os fatores desencadeantes.

Medicamentoso

A droga de escolha para o tratamento das EGI é o valproato. Este medicamento controla todas as crises em até 80% dos pacientes com epilepsia ausência, 97% dos pacientes com EMJ e 85% dos pacientes com CTCG [JANZ e DURNER, 1997; PANAYIOTOPOULOS, 1997; JANZ, 2000]. A etossuximida é utilizada especialmente para as crises de ausência. O controle das crises é semelhante ao valproato.

O valproato tem como efeitos adversos mais freqüentes tremores, queda de cabelo, ganho de peso e irregularidades menstruais. Além disso, este medicamento está associado a uma taxa mais elevada de malformações, principalmente defeitos do tubo neural, quando utilizados em gestantes.

Devido aos efeitos adversos do valproato, a lamotrigina é considerada por muitos a droga de escolha em pacientes jovens do sexo feminino. A lamotrigina tem um controle de crises semelhantes ao valproato, porém com menor número de efeitos adversos. A lamotrigina pode piorar a freqüência e intensidade de mioclonias sendo esta uma das maiores desvantagens na utilização em EGI.

De acordo com a literatura, carbamazepina e fenitoína não devem ser utilizados de forma rotineira na EGI. Estes medicamentos podem agravar as ausências, mioclonias e CTCG [PERUCCA, 1998; GENTON, 2000]. O uso inapropriado destas medicações em pacientes com EGI pode levar a uma maior dificuldade no controle das crises. Devido a este fato, alguns pacientes são rotulados como apresentando epilepsia refratária.

2- OBJETIVOS E METODOLOGIA

2.1- Objetivos

Objetivo geral

O objetivo geral deste estudo foi avaliar as características clínicas, eletroencefalográficas e de neuroimagem em um grupo de pacientes com EGI em um centro terciário (Hospital das Clínicas da Universidade Estadual de Campinas). Frente à avaliação destas características procuramos definir o mecanismo fisiopatológico presente nas EGI. Através da melhor definição do mecanismo destas patologias nosso objetivo incluiu verificar se as EGI constituem um grupo de patologias distintas ou se representam um *continuum biológico* entre si.

Objetivos específicos

Com relação aos objetivos específicos dividimos nosso estudo nas três partes principais abaixo descritas:

1- Avaliação clínica

O objetivo da avaliação clínica foi determinar, sobretudo o perfil demográfico e as características semiológicas das crises dos pacientes com EGI.

2- Avaliação eletroencefalográfica

Delimitar o perfil eletroencefalográfico de rotina de pacientes com EGI. Avaliar as alterações que poderiam levar a um possível erro no diagnóstico. Investigar a presença de focalidades no EEG interictal de pacientes com EGI.

3- Avaliação por neuroimagem

O objetivo específico da avaliação por neuroimagem foi avaliar pacientes com EGI utilizando a RM de alta resolução. Inicialmente realizamos a avaliação por análise visual para investigar anormalidades estruturais maiores. Além disso, procuramos relacionar a neuroimagem com as alterações no EEG. Em seguida, utilizamos análises

quantitativas para procurar por anormalidades estruturais sutis. A MBV foi realizada inicialmente procurando por diferenças entre as três principais subsíndromes de EGI. Finalmente, após a MBV utilizamos a volumetria convencional para quantificar algumas das anormalidades evidenciadas na MBV.

2.2- Metodologia

Aspectos éticos

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP (anexo 1) e oferece riscos mínimos aos pacientes. Este estudo faz parte de outro projeto temático para estudo de neuroimagem nas epilepsias também aprovado pelo comitê de ética.

Todos os indivíduos participantes deste estudo foram devidamente esclarecidos quanto à finalidade da pesquisa, através de formulários de consentimento informado (anexos 2).

Identificação dos pacientes

Todos os pacientes exclusivamente com crises generalizadas em seguimento no ambulatório de epilepsia do Hospital das Clínicas UNICAMP foram selecionados. A história clínica foi detalhada com todos os pacientes e com pelo menos uma pessoa que tenha observado pelo menos uma crise típica do paciente.

Definição de epilepsia generalizada idiopática

O diagnóstico de EGI foi realizado baseado na história clínica. Os pacientes foram sistematicamente questionados sobre a presença dos três tipos de crises generalizadas. Procuramos também por outras características sugestivas de EGI como história familiar, fatores desencadeantes (sobretudo privação de sono e uso de bebidas alcoólicas), relação das crises com o ciclo sono-vigília e farmacodependência (especialmente recidivas de crises depois da retirada do medicamento).

Definimos como história familiar positiva a presença de pelo menos um parente de primeiro ou segundo grau com história compatível com epilepsia.

Classificação clínica dos pacientes

A classificação foi realizada de acordo com recomendações da literatura [ILAE 1989; ANDERMANN e BERKOVIC, 2001; CUTTING et al., 2001; PANAYIOTOPOULOS, 2002; MARINI et al., 2003].

- **Epilepsia do tipo ausência:** pacientes com claro predomínio das crises do tipo ausência. Neste grupo incluímos principalmente pacientes com epilepsia ausência juvenil.

- **Epilepsia mioclônica juvenil:** pacientes com predomínio de crises mioclônicas.

- **Epilepsia com crises tônico-clônicas generalizadas:** pacientes com crises do tipo tônico-clônicas generalizada predominado de forma absoluta.

Critérios de exclusão

O principal critério de exclusão foi a história clínica ou o exame neurológico sugestivo de crises parciais.

Avaliação eletroencefalográfica

Todos os pacientes foram submetidos ao registro eletroencefalográfico de 20-30 minutos com hiperventilação e fotoestimulação intermitente em um aparelho de 16 ou 32 canais. Utilizamos o sistema internacional 10-20 para a colocação de eletrodos. O exame foi realizado no estado interictal sem privação de sono.

Os exames foram classificados em três grupos:

- **Com anormalidades generalizadas típicas:** neste grupo foram incluídos os EEGs com complexos espícula onda lenta regulares ou irregulares síncronos exacerbados ou não pela fotoestimulação e hiperventilação;
- **Com anormalidades generalizadas atípicas:** EEGs com ondas agudas ou ondas lentas focais bem definidas, focalidades ou assimetrias (especialmente de freqüência e amplitude). Os pacientes que apresentavam anormalidades típicas e atípicas no mesmo exame foram classificados como atípicos;
- **Normal.**

Avaliação com ressonância magnética

As imagens foram obtidas em um aparelho de 2.0T (Elscint Prestige®). Utilizamos um protocolo previamente definido incluindo: **(a)** *sagital* T1 "spin-echo", 6mm de espessura (TR=430, TE=12) para melhor orientação das imagens subseqüentes. **(b)** *coronal* T1 "inversion recovery", 3mm de espessura (flip angle=200º; TR=2800-3000, TE=14, "inversion time" [Tl]=840, matriz=130×256, FOV=16×18 cm). **(c)** *coronal* ponderadas em T2 "fast spin echo" (FSE), 3-4mm de espessura, (flip angle=120º, TR=4800, TE=129, matriz=252×320, FOV=18×18cm). **(d)** *axial* com imagens paralelas ao longo eixo do hipocampo; T1 "gradient echo" (GRE), 3mm de espessura (flip angle=70º, TR=200, TE=5, matriz=180×232, FOV=22×22cm). **(e)** *axial* T2 FSE, 4mm de espessura, ângulo de excitação=120º, TR=6800, TE=129, matriz 252×328, FOV=21×23cm. **(f)** *Volumétrico* (3D) T1 GRE adquirido no plano sagital com 1mm de espessura (flip angle=35°, TR=22, TE=9, matriz=256×220, FOV=23×25cm).

Análise visual

Todas as seqüências acima foram avaliadas. Todas as anormalidades observadas foram relacionadas. As anormalidades foram posteriormente classificadas de acordo com os achados.

Morfometria baseada em voxel

Para realizar a MBV as imagens são previamente processadas de acordo com o protocolo do laboratório de neuroimagem da UNICAMP. Este protocolo foi baseado na metodologia descrita por GOOD et al. (2001).

As imagens adquiridas encontram-se no formato DICOM. Utilizamos o programa MRIcro (www.mricro.com, RORDEN e BRETT, 2000) para transformar as imagens no formato ANALYZE. Em seguida utilizamos este mesmo programa para localização da comissura anterior.

Utilizando o programa SPM2 (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) as imagens são normalizadas, segmentadas e suavizadas [FRISTON et al, 1995]. De acordo com o protocolo descrito por GOOD et al. (2001) realizamos também a modulação das imagens.

- **Normalização:** as imagens são passadas para o espaço padrão para reduzir a variabilidade interindividual do tamanho da cabeça. A normalização é baseada em um ponto em comum (comissura anterior) e utiliza transformações lineares e não lineares. Este passo é realizado de acordo com uma imagem padrão.
- **Segmentação:** o programa SPM dispõe de rotinas que automaticamente segmentam a substância cinzenta das imagens. A segmentação estima a probabilidade de cada voxel ser substância cinzenta.
- **Modulação:** esta etapa preserva a quantidade de tecido que eventualmente tenha sido deformado pela normalização.
- **Suavização:** realizada com um filtro isotrópico Gaussiano de 10 mm. Este passo reduz a variação dos sulcos e giros fazendo com que as imagens apresentem uma distribuição mais normal permitindo a comparação posterior entre as mesmas.

Volumetria

A análise volumétrica do tálamo foi realizada utilizando o programa Display (desenvolvido pelo Brain Imaging Center; Montreal Neurological Institute; Montreal, Que, Canadá). As imagens foram previamente processadas para correção da

inomogeneidade de campo e para transformação linear para o espaço padrão com intuito de reduzir a variabilidade interindividual.

Os tálamos foram manualmente segmentados utilizando limites anatômicos previamente estabelecidos [BERNASCONI et al, 2003; NATSUME et al, 2003].

Apresentação e análise dos dados

Os achados referentes à investigação dos pacientes com EGI estão apresentados na forma de artigos. Cada aspecto da avaliação recebeu enfoque específico e os resultados estão apresentados no capítulo 3.

Inicialmente realizamos a investigação e avaliação eletroencefalográfica dos pacientes com EGI estas características estão descritas no artigo 1.

Após observarmos a presença de elementos focais no EEG de nossos pacientes, realizamos o artigo 2 relacionando os achados da análise visual com o EEG. Em decorrência das anormalidades sutis descritas no artigo 2, utilizamos técnicas quantitativas para estudar as imagens.

A MBV foi realizada procurando por anormalidades nas imagens dos pacientes com EGI que não apresentaram alteração na análise visual (artigo 3). Em seguida, realizamos a avaliação dos pacientes com focalidades no EEG utilizando novamente a MBV (artigo 4). Frente aos resultados obtidos pela MBV e amparados pela literatura decidimos realizar o estudo volumétrico do tálamo nos pacientes investigados (artigo 5).

3- RESULTADOS

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EEG Features in Idiopathic Generalized Epilepsy: Clues to Diagnosis

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Summary: *Purpose:* To investigate the EEG profile and its contribution for diagnosis and management in a group of patients with a clinical diagnosis of idiopathic generalized epilepsy (IGE) who were referred to a tertiary hospital.

Methods: We retrospectively studied clinical and EEG features of 180 consecutive patients with IGE. Eighty patients were diagnosed with juvenile myoclonic epilepsy (JME), 35 had absence epilepsy (AE), 13 had generalized tonic–clonic seizures on awakening (GTCS-A), 28 had generalized tonic–clonic seizures only (TCS), and 24 had adult-onset idiopathic generalized epilepsy (AIGE). The EEGs were classified in typical (synchronous generalized spike or polyspikes-and-wave discharges with normal background), atypical (with clear focalities or asymmetries), and normal.

Results: The 493 EEG exams were analyzed. The first EEG was normal in 45% of the 180 patients, and only 33% had typical abnormalities. AE had a higher proportion of typical examinations and needed fewer sequential examinations to register a typical abnormality compared with the other groups. By contrast, the serial EEG profile of TCS and AIGE showed a higher proportion of normal and atypical EEG findings.

Conclusions: These findings support previous recommendations that IGE patients should be treated with appropriate therapy based on clinical history. Waiting for a typical abnormal EEG pattern can generate an unacceptable delay in the correct diagnosis and treatment of these patients. In patients with long-term epilepsy, the diagnosis may be difficult. Furthermore, serial EEGs can help to elucidate the syndromic diagnosis, especially in patients with TCS and AIGE. **Key Words:** Idiopathic generalized epilepsy—EEG—Diagnosis.

Idiopathic generalized epilepsies (IGEs) correspond to 20–40% of all epilepsies (1–3). Despite their frequency, IGEs remain underdiagnosed (4). IGEs are divided according to the age at onset and the main types of seizures in five main subsyndromes: childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy (JME), and generalized tonic–clonic seizures only, which includes generalized tonic–clonic seizures on awakening, during sleep, and at random distribution (5,6). Adult-onset IGE (AIGE) is considered a subsyndrome of the IGE (7,8). A frequent overlap exists between these syndromes, and sometimes the distinction is complex (9).

Typical findings in the electroencephalograms (EEGs) of patients with IGE are bilateral, synchronous generalized spike-and-wave (GSW) or polyspikes-and-wave discharges with normal background. Some characteristic EEG patterns are associated with different IGE syndromes; however, these are nonspecific (10). In addition, asymmetries and pseudofocalities may occur in some EEGs of IGE patients (11–13).

It is generally accepted that diagnosis and subsequent treatment should be made according to clinical and EEG criteria. However, waiting for a typical abnormal EEG pattern to appear may be time consuming and a luxury that the clinician does not have when a therapeutic decision is immediately required.

The purpose of this study was to investigate the first and serial EEG findings in patients with distinct IGE subsyndromes who were referred to a tertiary hospital to look for clues that may help the clinician in the decision-making process. The intention of the study was not evaluate the EEG in newly diagnosed patients. This study also reports patients that are under treatment and investigation. Therefore this study reflects our daily practice with patients with epilepsy, and we believe that this is clinically relevant.

METHODS

We included all patients with generalized seizures compatible with IGE seen in our epilepsy clinics over the last 5-year period. Patients and at least one person who watched

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typical seizures were reinterviewed for this study. Patients with suspected partial epilepsy or evidence of seizures with focal onset were excluded. Medical records as well as all available EEG tracings were reevaluated.

All patients and relatives were systematically questioned for the presence of epilepsy in the family. Family history was considered positive when at least one first- or second-degree relative had a history of generalized seizures.

IGE syndromes were classified according to the International League Against Epilepsy (ILAE) 1989 recommendations and by publications on adult-onset IGE (5–7). Patients were divided into JME, absence epilepsy (AE), which included childhood and juvenile absence epilepsies, generalized tonic–clonic seizures on awakening (GTCS-As), generalized tonic–clonic seizures only (TCSs), and adult-onset idiopathic generalized epilepsy (AIGE). Patients were classified in the TCS group when GTCSs occurred at any time of the day without a clear relation to awakening or a leisure period. High-resolution magnetic resonance imaging (MRI) was performed in 170 patients (73 JME, 33 AE, 12 GTCS-A, 28 TCS, and 24 AIGE). All patients in the TCS and AIGE groups had normal MRIs.

We recorded a 20- to 30-min EEG exams with hyperventilation and intermittent photic stimulation in a 16- or 32-channel EEG recorder. We used the international 10-20 system for electrode placement. Exams were performed in the interictal state without sleep deprivation.

The first EEG was recorded at our service ranging from 0 to 44 years after seizure onset. The records were divided into three groups according to the number of years after the first seizure that the EEG was performed (0 to 5 years, 6 to 10 years, and 11 years and more). Comparisons between these groups were done to evaluate whether different characteristics in the EEGs exist. Duration of epilepsy was defined as the difference between the first and the last seizure.

EEGs were classified into three groups:

- With typical generalized features: in this group, we included EEGs with irregular or regular synchronous GSW pattern exacerbated or not by photic stimulation and hyperventilation;
- With atypical generalized features (Fig. 1): EEGs with well-defined sharp or slow waves, focalities, and asymmetries (especially frequency and amplitude). Patients with typical and atypical findings in the same record were classified as atypical;
- Normal.

Survival curves with data on serial EEG tracings were constructed based on the number of typical abnormalities. For statistical analysis, we used χ^2 and Fisher's tests. The curves were compared by using the Mantel–Haenszel test. The level of statistical significance was defined as a p value <0.05.

RESULTS

We included 180 consecutive patients (101 women) with clinical diagnosis of IGE. Mean age at first evaluation was 31.1 years (range, 8–79 years). Patients were referred from primary care centers or general practitioners. Initially, 35 (19%) and five (3%) patients were taking valproate (VPA) and lamotrigine (LTG), respectively, when the first EEG was performed, 126 (70%) patients were taking antiepileptic drugs (AEDs) other than VPA or LTG, and 14 (8%) were without AEDs.

At the time of clinical evaluation for the present study, 105 (58%) patients were taking VPA or LTG or both, and 145 (80%) patients were seizure free for $\geq$1 year.

In total, 493 EEGs were evaluated. Tables 1 and 2 summarize clinical and EEG findings.

First EEGs

Among the 180 first EEGs examined, 82 (45%) were normal, 98 (55%) were abnormal, but only 58 (33%) showed typical abnormalities.

Among the EEGs performed 0 to 5 years after the first seizure, 24 (30%) had typical abnormalities, 15 (19%) had atypical abnormalities, and 41 (51%) were normal. From 6 to 10 years after the first seizure, 15 (39%) had typical abnormalities, nine (24%) had atypical abnormalities, and 14 (37%) were normal. From 11 years and beyond, 20 (32%) had typical abnormalities, 16 (26%) had atypical abnormalities, and 26 (42%) were normal. No difference was found between the proportions of typical abnormalities among these three groups.

JME ($n = 80$)

A family history of epilepsy was present in 53 (66%) patients. Mean age of patients at evaluation was 30.3 years, and mean age at seizure onset was 12.2 years. The first EEGs examinations were normal in 35 (44%) of these, showed atypical abnormalities in 16 (20%), and had typical abnormalities in 29 (36%). The first EEG was performed in average 9.9 $\pm$ 8.8 (0–39) years after the first seizure, and the mean duration of the epilepsy was 14.1 $\pm$ 10 (0–47) years.

AE ($n = 35$)

A family history of epilepsy was present in 24 (68%) patients. The mean age of patients at evaluation was 26, and the mean age at seizure onset was 8.8 years. The first EEGs were normal in seven (20%), had atypical abnormalities in nine (26%), and had typical findings in 19 (54%). The first EEG was performed on average 9.1 $\pm$ 9.1 (0–34) years after the first seizure, and the mean duration of the epilepsy was 14.8 $\pm$ 11.6 (0–43) years.

GTCS-A ($n = 13$)

A family history of epilepsy was present in eight (61%) patients. The mean age of patients at evaluation was 27.3 years, and the mean age at seizure onset was 11.8 years.

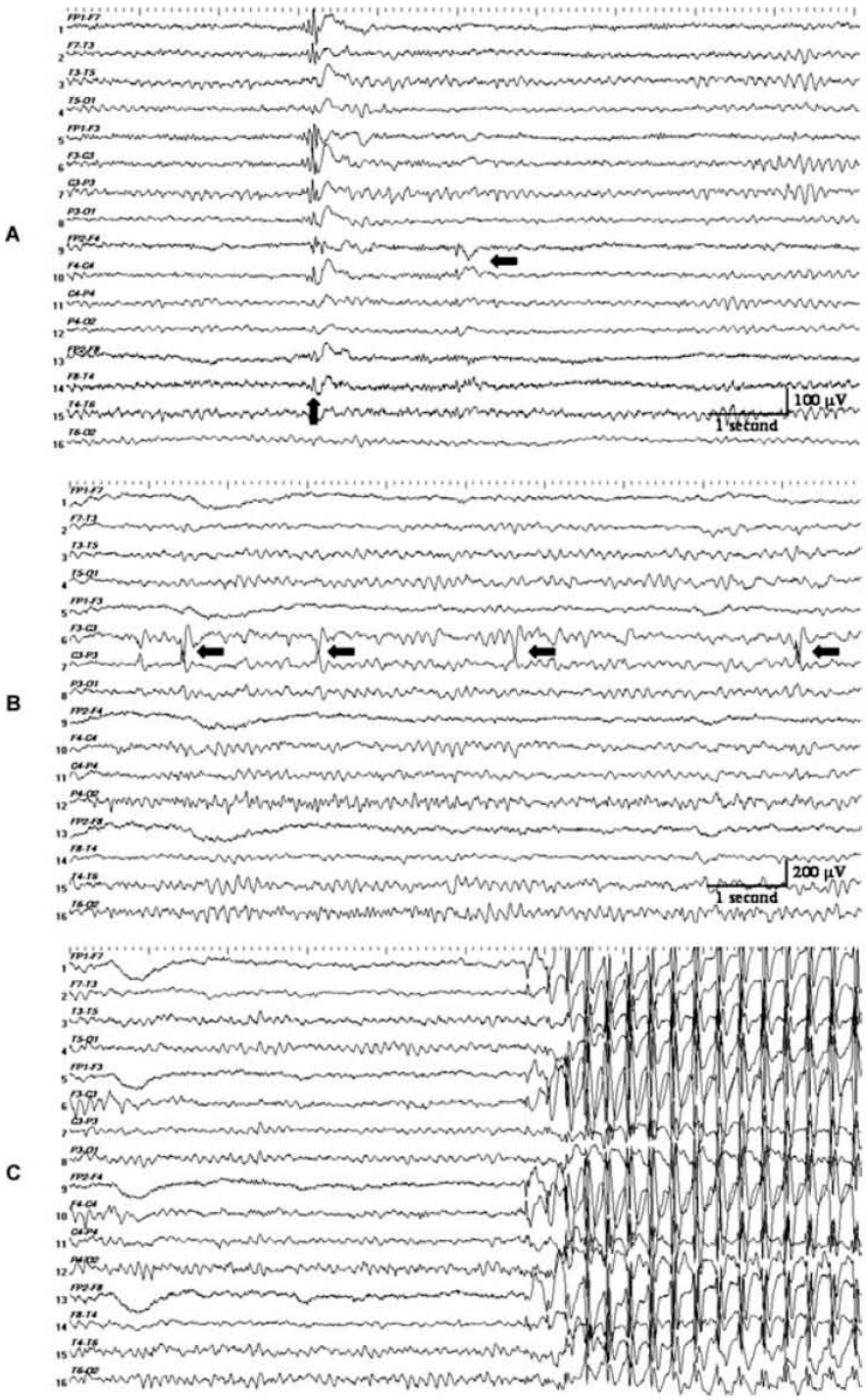

FIG. 1. Examples of atypical findings in patients with idiopathic generalized epilepsy (IGE). **A:** Generalized asymmetrical polyspikes-and-wave discharge (*vertical arrow*) followed by a focal spike-and-wave discharge with phase reversal in the right frontal region (*horizontal arrow*) in the longitudinal bipolar montage. Referential montages confirmed the asymmetry. This patient has history of generalized tonic–clonic seizures since age 18 years. Two years later, frequent absences seizures began. **B, C:** Longitudinal bipolar montages of a 9-year-old girl with typical absence seizures. This record showed left centrotemporal spikes (**B**; *horizontal arrows*), and ~50 s later, a typical regular generalized spike-and-wave discharge **(C)**. EEG settings, high filter, 70 Hz; time constant, 0.3.

TABLE 1. *Demographic data of 180 patients with idiopathic generalized epilepsy*

	No.	M	W	Family history	Age (yr, range)	Seizure onset (yr, range)
JME	80	32	48	53 (66%)	30.3 ± 9.2 (17–63)	12.2 ± 3.8 (2–20)
AE	35	14	21	24 (68%)	26 ± 12 (8–62)	8.8 ± 4.8 (1–19)
GTCS-A	13	4	9	8 (61%)	27.3 ± 12 (14–52)	11.8 ± 4 (5–18)
TCS	28	17	11	19 (68%)	30.9 ± 11.5 (15–61)	10.4 ± 5.5 (1–19)
AIGE	24	12	12	14 (58%)	43.3 ± 15.5 (23–79)	33.1 ± 14.4 (21–70)
Total	180	79	101	118 (65%)	31.1 ± 12.3 (8–79)	14.1 ± 10.1 (1–70)

Age at evaluation and seizure onset expressed in mean years ± standard deviation (range).
No., number of patients; M, man; W, woman; JME, juvenile myoclonic epilepsy; AE, absence epilepsy; GTCS-A, generalized tonic–clonic seizure on awakening; TCS, generalized tonic–clonic seizures only; AIGE, adult-onset idiopathic generalized epilepsy.

The first EEGs were normal in six (46%), had atypical abnormalities in three (23%), and had typical abnormalities in four (31%). The first EEG was performed on average 8.3 ± 11.4 (0–33) years after the first seizure, and the mean duration of the epilepsy was 9.7 ± 11 (0–43) years.

TCS (n = 28)

A family history of epilepsy was present in 19 (68%) patients. The mean age of patients at evaluation was 30.9 years, and the mean age at seizure onset was 10.4 years. The first EEGs were normal in 15 (54%) patients, had atypical abnormalities in nine (32%), and typical abnormalities in four (14%). The first EEG was performed on average 11.3 ± 11.1 (0–44) years after the first seizure, and the mean duration of the epilepsy was 15.7 ± 11.8 (0–50) years.

AIGE (n = 24)

A family history of epilepsy was present in 14 (58%) patients. The mean age of patients at evaluation was 43.3 years, and the mean age at seizure onset was 33.1 years. The first EEGs were normal in 19 (79%) patients, had atypical abnormalities in three (13%), and typical abnormalities in two (8%). The first EEG was performed on average 4.3 ± 5.6 (0–24) years after the first seizure, and the mean duration of the epilepsy was 6.3 ± 7.7 (0–33) years.

AE had a higher proportion of initial typical exams compared with the other groups ($p = 0.002$). Conversely, TCS and AIGE had a higher number of initial atypical and normal exams compared with the others ($p = 0.029$ and $p = 0.008$, respectively).

Serial EEGs

A mean of 2.7 ± 2.1 (1–14) exams per patient were performed, and the distribution among the groups was JME, 2.4 ± 1.6 (1–9); AE, 1.8 ± 1.4 (1–7); GTCS-A, 2.6 ± 1.9 (1–7); TCS, 3.8 ± 3 (1–14); and AIGE, 3.8 ± 2.7 (1–13).

Of the 180 patients, 38 (21%) had persistently normal EEGs on follow-up. The distribution of persistently normal EEGs among the groups was 14 (17.5%) of 80 patients in the JME group, one (3%) of 35 patients in the AE group, three (23%) of 13 patients in the GTCS-A group, seven (25%) of 28 patients in the TCS group, and in 13 (54%) of 24 patients in the AIGE group. Comparisons between the groups showed that AE had a lower number of persistently normal EEGs ($p = 0.002$), and AIGE had a higher number of persistently normal exams ($p < 0.001$).

Analysis of the serial EEGs showed that patients with AE needed fewer sequential EEG tracings to register a typical abnormality ($p < 0.001$). By contrast, the serial EEG profile of TCS and AIGE showed a higher number

TABLE 2. *First and serial EEG results according to clinical classification*

	Typical		Atypical		Normal		Total	
	First	Serial	First	Serial	First	Serial	First	Serial
JME	29 (36%)	18 (16%)	16 (20%)	33 (29%)	35 (44%)	62 (55%)	80	113
AE	19 (54%)	8 (26%)	9 (26%)	13 (42%)	7 (20%)	10 (32%)	35	31
GTCS-A	4 (31%)	3 (14%)	3 (23%)	5 (24%)	6 (46%)	13 (62%)	13	21
TCS	4 (14%)	4 (5%)	9 (32%)	24 (30%)	15 (54%)	51 (65%)	28	79
AIGE	2 (8%)	3 (4%)	3 (13%)	13 (19%)	19 (79%)	53 (77%)	24	69
Total	58 (33%)	36 (12%)	40 (22%)	88 (28%)	82 (45%)	189 (60%)	180	313

JME, juvenile myoclonic epilepsy; AE, absence epilepsy; GTCS-A, generalized tonic–clonic seizure on awakening; TCS, generalized tonic–clonic seizure only; AIGE, adult-onset idiopathic generalized epilepsy.

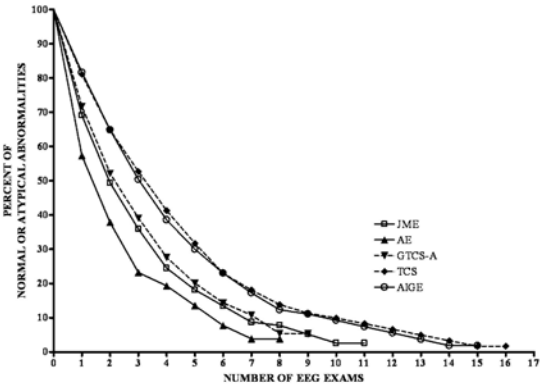

FIG. 2. Kaplan–Meier survival plots showing serial EEG records in patients with idiopathic generalized epilepsy (IGE). Initial EEGs in the AE group were less likely to be normal or with atypical abnormalities. By contrast, in TCS and AIGE groups, more exams were necessary to record a typical abnormality. JME and GTCS-A showed an intermediate pattern compared with the other groups ($p < 0.001$). JME, juvenile myoclonic epilepsy; AE, absence epilepsy; GTCS-A, generalized tonic–clonic seizure on awakening; TCS, generalized tonic–clonic seizures only; AIGE, adult-onset idiopathic generalized epilepsy.

of normal and atypical exams. JME and GTCS-A had an intermediate pattern (Fig. 2).

DISCUSSION

Diagnosis of epilepsy is based mainly on clinical history. However, the EEG may provide strong supportive evidence. More than 40% of patients with epilepsy may have one normal interictal EEG (14). Multiple EEG recordings and activating procedures such as recordings after sleep deprivation increase the probability of registering a typical interictal epileptiform activity (6,15,16). In addition, previous studies suggested that EEG abnormalities are more commonly observed in EEGs within the 24 h after a seizure (17–19).

The 180 patients included in the present study were referred from primary care centers with the possible diagnosis of epilepsy. Except for 14 patients, all were taking AEDs at the time of referral. However, at the time of the first EEG, 126 (70%) patients were receiving AED treatments other than VPA or LTG. These drugs are considered first-line therapies for IGE. Therefore the low frequency of abnormalities found in the first EEG recordings cannot be attributed to adequate treatment.

Our study showed that 58 (33%) of 180 first EEGs showed typical abnormalities. IGE will have a first abnormal and characteristic EEG in 54–81% of the patients with JME, and ≤90% in patients with untreated absence epilepsy (6,20). This contrast reflects the condition of the population studied. All patients were in a tertiary center. The first EEGs performed at our service ranged from 4.7 (AIGE) to 11.3 (TCS) years after seizures onset, on average. After years of disease, the EEG may become atypical or persistently normal, especially with remission of the epilepsy (6,21). In these situations, the diagnosis may be difficult, and special attention to the clinical history is required. Despite this, when the EEGs were divided according to the interval between the first recording and seizure onset, no significant differences were found between the groups.

In JME patients, 29 (36%) of 80 had generalized discharges in the first EEG. A high rate of EEGs were found with normal [35 (44%) of 80] and atypical findings [16 (20%) of 80]. Focal findings may be present in 20% of the initial records in JME (22). Of the patients with JME, 84% will have generalized discharges in the first three records. This rate increase to 96% in patients with four to eight recordings and remains unchanged after the eighth record (20). Our results have important implications for the treatment of JME, because they indicate that it may be difficult to select the most adequate AED regimen based primarily on EEG findings in patients with suspected IGE. The lower rate of typical EEG findings (36%) calls attention to the importance of the clinical history, especially in patients with ongoing epilepsy and inappropriate treatment. Incorrect therapy with uncontrolled seizures may cause physical and psychosocial morbidity in an otherwise benign condition (23).

By contrast, AEs had the lowest rate of first normal EEGs (20%). Absences are easily studied with the EEG because improperly treated patients usually have the typical abnormalities on EEG recording. The EEG will confirm the diagnosis in >90% of untreated patients, mainly during hyperventilation (6,21). Probably the inadequate treatment of patients with AE contributed to the lower rate of first normal EEG.

GTCSs can be divided according to the relation between the seizures and the sleep–waking cycle (6,24). The first EEG was typical in 31% of the patients with GTCS-A. Conversely, the TCS group had a lower rate of first typical examinations (14%). In the TCS group, we included patients with GTCS occurring predominantly at sleep and randomly. In the latter clinical course of the GTCS-A, the seizures may predominate during sleep. The EEGs of patients with GTCS during sleep contrast with those of patients with GTCS-A. Patients with GTCSs during sleep have a higher frequency of normal EEGs (24). Probably these differences were reflected in our findings.

Focal epilepsy must be considered and properly investigated in adults with new seizure onset. However, a growing number of publications concern AIGE (7,8,10,25–29). This syndrome, similar to classic IGE, also has been divided into subtypes according to the predominant types of seizures. Despite of the identification of absence and myoclonic seizures, GTCSs alone appear to be the main seizure type. The hallmarks are the benign clinical course with easy AED control and EEGs markedly normal, as

observed in our patients with AIGE (54% had persistently normal interictal EEGs) (8,10).

Serial EEG recordings showed a different profile among the different IGEs. Typical abnormalities were found earlier in AE as opposed to TCS and AIGE, which needed more recordings to register a typical abnormality.

The pathophysiology of the IGE remains under investigation. Experimental studies are showing that probably a cortical focus is responsible for the discharge onset, and the interaction between this focus and the thalamus is critical for seizure maintenance (30). Focalities disclosed by the EEG may reflect mild cortical structural abnormalities in patients with IGE. Modern MRI techniques are supporting this hypothesis, showing structural abnormalities in patients with IGE (31,32). A new definition of this group of IGE patients will be necessary. The relation between these focalities and treatment failures are unclear. However, previous works pointed to a higher rate of refractory seizures in patients with EEG focalities (32). In our study, 80% of patients were seizure free for ≥1 year.

These findings reinforce that AED treatment of the different types of IGEs should be chosen according to clinical history. Waiting for typical EEG abnormalities can generate an even longer delay in the correct treatment of patients with IGE.

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MRI reveals structural abnormalities in patients with idiopathic generalized epilepsy

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MRI reveals structural abnormalities in patients with idiopathic generalized epilepsy

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Abstract—*Objective:* To evaluate MRI findings in a large group of patients with idiopathic generalized epilepsies. *Methods:* Idiopathic generalized epilepsies were diagnosed according to clinical and EEG criteria following International League Against Epilepsy recommendations. MRI was performed in a 2.0 T scanner using a previously established epilepsy protocol. Images were reviewed, and any abnormality was reported. Patients were divided in those with and without MRI abnormalities. Comparisons were made between these groups concerning age, age at seizure onset, subsyndrome, EEG findings, and seizure control. *Results:* Of the 134 MRIs evaluated, 33 (24%) showed abnormalities, most of which (88%) were nonspecific. There were eight main abnormalities: arachnoid cyst, diffuse cortical atrophy, basal ganglia abnormalities (signal alterations and prominent perivascular spaces), ventricular abnormalities (uni- or bilateral increased volume of the lateral ventricles), white matter abnormalities (increased T2 signal in the frontal lobes), reduced hippocampal volume, focal gyral abnormality, and area of gliosis in the frontal lobe. Comparisons between the groups showed a higher proportion of EEG focalities in patients with abnormal MRI, which were in most part concordant with the location of the MRI abnormalities. *Conclusions:* Twenty-four percent of patients with idiopathic generalized epilepsies had MRI abnormalities. However, the majority of these abnormalities were nonspecific.

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The underlying mechanism of seizure generation in idiopathic generalized epilepsies (IGEs) remains controversial. EEG studies suggest the onset of generalized spike-and-wave (GSW) discharges located in the frontal cortex, whereas other studies showed a thalamic onset of GSW before neocortex involvement.[1,2] A cortical hyperexcitability also may play an important role in the generation of seizures in these patients.[3]

Visual assessment of MRI in patients with IGE is expected to be normal.[4] However, in a few patients, there are descriptions of structural abnormalities leading to seizures resembling IGE.[5,6] In this study, we investigated MRI findings in a large group of patients with IGE.

Methods. *Subjects.* We prospectively studied 134 consecutive patients with clinical history of generalized seizures at our epilepsy clinics over the last 5 years. Patients with suspected focal seizure onset were excluded. Patients over age 50 were not included because of some findings such as cerebral atrophy and ischemic lesions are more frequent in this age group. Classification was made based on clinical and EEG criteria according to the International League Against Epilepsy and the current literature.[7,8] All patients were interviewed along with at least one person who previously witnessed a typical seizure. All patients underwent MRI. All patients signed informed consent approved by the local ethics committee. Medical records prior to patients' inclusion were also reviewed.

MRI scanning protocol and evaluation. MRI was performed using a 2.0 T scanner (Elscint, Haifa, Israel). A previously defined protocol was used, including 1) sagittal T1 spin echo, 6 mm thick (repetition time [TR] = 430 milliseconds, echo time [TE] = 12 milliseconds) for optimal orientation of the subsequent images; 2) coronal T1 inversion recovery, 3 mm thick (flip angle = 200°, TR = 2,800 to 3,000 milliseconds, TE = 14 milliseconds, inversion time TI = 840 milliseconds, 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 = 4,800 milliseconds, TE = 129 milliseconds, 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 milliseconds, TE = 5 milliseconds, matrix = 180 × 232, FOV = 22 × 22 cm); 5) axial fluid-attenuated inversion recovery (FLAIR), 4 mm thick (flip angle = 110°, TR = 10,099 milliseconds, TE = 90 milliseconds, matrix = 250 × 250, FOV = 24 × 234 cm); 6) volumetric (three-dimensional) T1 GRE acquired in the sagittal plane with 1 mm thick (flip angle = 35°, TR = 22 milliseconds, TE = 9 milliseconds, matrix = 256 × 220, FOV = 23 × 25 cm) for multiplanar reconstruction. MRI evaluation was performed in a computer workstation. All available images and multiplanar reconstruction were visually analyzed blindly to the clinical information. We searched for any anatomic abnormalities. The abnormalities were classified in groups based on the findings.

Hippocampal volumetry was performed in all patients. These volumes were compared with those from a group of 42 healthy control subjects (20 women, mean age 29 ± 9 years, range 14 to 50 years). This quantitative assessment was performed essentially to

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confirm hippocampal abnormalities eventually described in the visual inspection. The three-dimensional sequence with 1 × 1 × 1–mm voxel size was used for volumetry.

After acquisition, images were automatically registered into stereotaxic space.[9] This process reduces the differences between total brain volumes and orientation allowing analysis between individuals. This procedure also facilitates the identification of anatomic boundaries by minimizing variability in slice orientation.[10] After this, images were submitted to a correction for field inhomogeneity and intensity standardization. This correction produces more consistent relative gray matter, white matter, and CSF intensities.[11] The hippocampi were manually delineated using the software Display (Brain Imaging Center, Montreal Neurologic Institute, Canada), following an anatomic protocol described previously.[12] All measures were performed by the same investigator after a training period. Volumes were expressed in cubic millimeters.

The volumes obtained for each individual were standardized according to the value of normal controls using a *Z*-score transformation. This transformation indicates that if a patient had a *Z*-score of −1, this patient had a volume that was 1 SD below the mean of normal controls. Asymmetry index defined as (l − R)/([L + R]/2) was obtained for all subjects and also was standardized according to the control volumes. We considered abnormal (hippocampal atrophy) when the volumes or the asymmetry index was more than 2 SD below the mean of controls.

EEG recording protocol. A 20- to 30-minute exam was obtained with hyperventilation and intermittent photic stimulation in 16- or 32-channel EEG recorder. The International 10–20 System for electrode placement was used. Exams were performed in interictal state. Sleep deprivation was not used. EEGs were classified in three groups: with typical GSW discharges: in this group, we included EEGs with irregular or regular synchronous GSW pattern exacerbated or not by photic stimulation and hyperventilation; with atypical generalized features: EEG with well defined sharp or slow waves (focalities and asymmetries were included in this group); normal EEG.

Statistical analysis. Comparisons between patients with and without MRI abnormalities were performed. Differences between age, age at seizure onset, time since last seizure, number of patients with abnormalities in each subsyndrome, and abnormalities on EEG were investigated. We used the χ^2 and Fisher exact test to analyze differences in proportions and Student *t* test to analyze mean differences between groups.

We used the Pearson correlation test to investigate the relationship between hippocampal volumes and duration of epilepsy (defined as the time between the first and the last seizure). The level of significance selected was $p < 0.05$.

Results. We evaluated 134 consecutive patients (83 women) with IGE. Family history was positive in 97 patients (72%). Distribution among the subsyndromes was 71 patients with juvenile myoclonic epilepsy (JME), 41 patients with generalized tonic-clonic seizures only (GTCS), and 22 patients with absence epilepsy (AE). Among the patients with AE, 17 had juvenile absence epilepsy and 5 childhood absence epilepsy. Thirty-three (24%) MRI exams showed abnormalities, most of which (88%) were nonspecific. The abnormalities were found in 19 of 71 patients with JME, 2 of 22 with AE, and 12 of 41 with GTCS. Twenty-six patients had only one abnormality, six had two, and one had three abnormalities.

Eight main abnormalities were found: arachnoid cyst, diffuse cortical atrophy, basal ganglia abnormalities, ventricle abnormalities, white matter abnormalities, reduced hippocampal volume, focal gyral abnormality, and area of gliosis in the frontal lobe.

Arachnoid cysts (two patients) were found in two patients with JME. They were located at the left middle (anterior to the temporal lobe with a maximum diameter on coronal section of 74 mm) and posterior fossa (posterior to the cerebellum and the occipital lobes with a maximum diameter on coronal section of 78 mm).

Diffuse cortical atrophy (six patients) was defined by diffuse prominence of cerebral sulcus and gyrus. Diffuse cortical atrophy was found in four patients with JME and in two patients with GTCS. Three patients were under valproate therapy. There were no cognitive abnormalities in these patients.

Basal ganglia abnormalities (nine patients) were found in five patients with JME and in four patients with GTCS. The abnormalities were areas of signal alterations and prominent perivascular spaces. Signal alterations were characterized by T2 hyperintense and T1 hypointense signal. These signal abnormalities were located at the globus pallidus (one JME), left insula (one JME), and thalamus (one GTCS). In one patient with GTCS, there was an isolated area of increased signal localized in the left insula observed only in the FLAIR sequence. Prominent perivascular spaces were located at the inferior portion of the left thalamus (one JME), lenticular nucleus and substantia innominata (one JME), caudate nucleus (one GTCS), putamen (one JME), and right internal capsule, lenticular nucleus, and left insular white matter (one GTCS). In all patients, perivascular spaces had signal intensity comparable with the CSF. The diameter observed in coronal sections ranged from 2 to 10 mm.

Ventricles abnormalities (six patients) in all patients were characterized by increased volume of one or both lateral ventricles evaluated by visual inspection. In one patient with GTCS, there was asymmetry of the lateral ventricles and in five patients, they were enlarged (five patients with JME). In the patient with ventricular asymmetry, the left lateral ventricle was enlarged; the difference between the two sides evaluated in the axial slices was 37%.

White matter abnormalities (four patients) were found in three patients with JME and one with AE. In all patients, the abnormalities were small lesions hyperintense on T2 and hypointense on T1-weighted images, located in the white matter. In two patients with JME, there were multiple areas of abnormalities localized bilaterally at the frontal lobes. There was a single lesion localized at the left frontal lobe in one patient with AE and at the right frontal lobe in one patient with JME.

In focal gyral abnormality in the frontal lobe (three patients, all with GTCS), the suspected abnormality was a profound cortical gyrus resembling cortical dysplasia. The suspected area was present in at least two contiguous MRI slices.

Area of gliosis in the frontal lobe was found in one patient with GTCS.

Reduced hippocampal volumes were found in 10 patients. With use of qualitative analysis, two patients had left hippocampal volume reduction (two GTCS), two right (one GTCS and one with JME), and two bilateral reduction (one JME and one AE). In only one patient with right hippocampal reduction, there was also T2 hyperintense signal. In these patients, the volume of the fornix ipsilateral to the hippocampal reduction was not decreased.

The mean hippocampal volumes of the control subjects were 3,354 ± 344 mm^3 (mean ± SD, range 2,606 to 3,937 mm^3) for the left and 3,334 ± 336 mm^3 (range 2,502 to 3,978 mm^3) for the right. The mean left and right hip-

Table 1 *Distribution of MRI abnormalities in patients with idiopathic generalized epilepsy*

Abnormalities	Juvenile myoclonic epilepsy	Absence epilepsy	GTCS	Total (n)
Arachnoid cyst	2	0	0	2
Diffuse cortical atrophy	4	0	2	6
Basal ganglia abnormalities	5	0	4	9
Ventricles abnormalities	5	0	1	6
White matter abnormalities	3	1	0	4
Reduced hippocampal volume	5	1	4	10
Focal gyral abnormality	0	0	3	3
Gliosis	0	0	1	1
Total (n)	24	2	15	41

Basal ganglia abnormalities were signal alterations and prominent perivascular spaces. Ventricles abnormalities were increased volume of the lateral ventricles (uni- or bilateral). White matter abnormalities were signal alterations (increased in T2) located in the frontal lobes.

GTCS = generalized tonic-clonic seizures only.

pocampal volumes in the IGE subsyndromes were 3,286 ± 391 mm^3 (range 2,678 to 3,852 mm^3) and 3,281 ± 355 (range 2,681 to 3,916 mm^3) for AE patients, 3,176 ± 350 mm^3 (range 2,312 to 3,969 mm^3) and 3,229 ± 364 (range 2,215 to 3,976 mm^3) for JME patients, and 3,154 ± 363 mm^3 (range 2,236 to 3,854 mm^3) and 3,150 ± 423 mm^3 (range 2,082 to 3,900 mm^3) for GTCS patients.

Hippocampal volumetry confirmed the atrophy disclosed by the visual analysis in all six patients. In addition, volumetry detected hippocampal atrophy in four patients in whom visual analysis was normal: Three had bilateral atrophy (one with GTCS and two with JME) and one JME patient had right hippocampal atrophy. The proportions of hippocampal atrophy were 4.5% (1/22) in the AE group, 5% (5/71) in the JME group, and 10% (4/41) in the GTCS group.

There was no correlation between hippocampal volumes and age, age at seizures onset, time since the last seizure, and duration of epilepsy ($p > 0.05$).

These results are displayed in table 1. The figure shows examples of these abnormalities.

In the group of patients with normal MRI (52 patients with JME, 20 with AE, 29 with GTCS), the mean age was

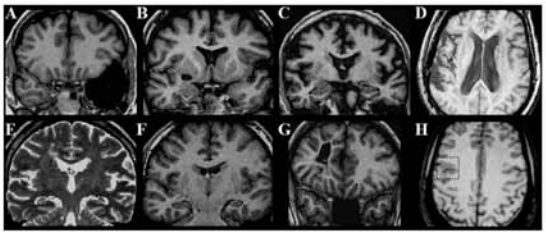

Figure. Eight main abnormalities in the MRI visual analysis of 134 patients with idiopathic generalized epilepsy. (A) Arachnoid cyst in the left temporal lobe. (B) Basal ganglia abnormalities. (C) Global cerebral atrophy. (D) Ventricles abnormalities. (E) White matter abnormalities. (F) Hippocampal asymmetry. (G) Area of gliosis in the frontal lobe. (H) Focal gyral abnormality in the frontal lobe.

Table 2 *Demographic data of 134 patients with idiopathic generalized epilepsy*

	MRI exam classification		
	Normal, n = 101	Abnormal, n = 33	Total
Sex distribution	63 F/38 M	20 F/13 M	134
Family history, n	74	23	97
Age	28 ± 9 (9–47)	30 ± 10 (17–50)	28 ± 9 (9–50)
Age at seizure onset	13 ± 7 (1–45)	13 ± 7 (1–35)	13 ± 7 (1–45)
Last seizure	3 ± 3 (0–20)	3 ± 3 (0–13)	3 ± 3 (0–20)
Classification			
Juvenile myoclonic epilepsy	52	19	71
Absence epilepsy	20	2	22
GTCS	29	12	41
EEGs*	414 (4)	166 (5)	580 (5)
EEG typical†	132	35	167
EEG atypical†	76	50	126
EEG normal	206	81	287

Time is expressed in years.

* Expressed at total (mean exams per patients).
† $p < 0.05$.

GTCS = generalized tonic-clonic seizures only.

28 ± 9 years (range 9 to 47 years) and the age at seizure onset was 13 ± 7 years (1 to 45 years). Time since the last seizure was 3 ± 3 years (0 to 20 years). In the group of patients with abnormal MRI (19 patients with JME, 2 with AE, and 12 with GTCS), mean age was 30 ± 10 years (range 17 to 50 years) and the age at seizure onset was 13 ± 7 years (1 to 35 years). Time since the last seizure was 3 ± 3 years (range 0 to 13 years). There was no difference between groups for these data ($p > 0.1$).

Five hundred eighty EEG records were analyzed. The mean number of exam per patient was 5 (range 1 to 14). In the group of patients with normal MRI, 414 EEG records were performed: 132 (32%) showed typical GSW discharges, 76 (18%) had focalities, and 206 (50%) were normal. In the group of abnormal MRI, 166 exams were performed: 35 (21%) showed typical GSW discharges, 50 (30%) had focalities, and 81 (49%) were normal.

In the group of abnormal MRI, 13 patients presented consistent focalities in at least two EEG records. These focalities persisted in serial EEG with an average of 5 ± 6 years (range 1 to 20 years). The EEG focalities coincided with the MRI abnormality in 70% (9/13) of the patients. Three of four patients with JME, five of eight patients with GTCS, and one of one patient with AE had the focalities congruent with the MRI findings. Comparisons between the patients with normal and abnormal MRI showed a higher number of EEGs with focalities ($p = 0.009$) and a lower rate of typical exams ($p = 0.002$) in patients with abnormal MRI. Table 2 summarizes the demographic data described above.

Discussion. By definition, MRI in patients with IGE is normal.[7] Ideally, all patients with epilepsy should undergo MRI evaluation. Despite this, MRI is not routinely recommended in patients with characteristic clinical and EEG features of IGE.[13] However,

advanced techniques in acquisition and processing of the images are allowing identification of subtle underlying structural and metabolic abnormalities in patients with IGE.[14,15] There are also descriptions of patients with heterotopies, vascular, inflammatory, and other cerebral insults, and a clinical picture resembling IGE. Periventricular and frontal lesions also may be associated with myoclonic and absence-like seizures.[5,6] The real frequency of structural abnormalities in patients with IGE is not clearly defined. The fact that MRI is not performed routinely in patients with typical IGE may help to underestimate the presence of small structural abnormalities in these patients. Signs of diffuse cortical atrophy may be present in patients with JME.[16] However, MRI and CT scans of these patients have not shown anything of etiologic relevance. In a study evaluating 82 patients with JME (22 with MRI), 13 (16%) had some type of structural abnormalities. The abnormalities were not clearly related to the seizures. The abnormal MRI did not influence therapeutic decisions and prognosis.[17] Another study investigated the clinical use of neuroimaging in 31 patients with IGE.[18] Fourteen patients had MRI and only one was submitted to high-resolution MRI with 1.5-mm slices. The author found abnormalities in only one patient, described as a single small nonspecific white matter lesion located at the brainstem. In the current study, all patients were submitted to a high-resolution MRI epilepsy protocol. This standardized protocol and the larger sample size may explain the higher frequency of abnormalities detected here.

Our study showed 24% of MRI abnormalities in patients with IGE. This frequency is elevated compared with the previous notion that all patients with IGE have normal MRI. Despite this high frequency, in only four patients (focal gyral abnormality and area of gliosis in the frontal lobe) the abnormality could be potentially epileptogenic. All other MRI findings appear to be incidental. However, compared with reports of incidental findings in MRIs of healthy individuals, our patients presented a higher rate of cerebral abnormalities. In a retrospective evaluation of 1,000 MRI scans in healthy adults, an investigation showed abnormalities in 18% of the population studied.[19] This percentage is similar to the 24% disclosed by our investigation. However, 13% of the abnormalities in that previous study[19] were sinusitis, which was not included in our study. Only 2% of the healthy individuals had incidental brain abnormalities.[19] Another study evaluating 225 MRI scans in a neurologically healthy pediatric population reported incidental findings in 47 patients (21%). The most prevalent finding was also sinusitis. Brain abnormalities were described in only 6% of the patients.[20]

Most of the structural abnormalities reported in our study are described in normal individuals and are more expected in elderly population.[21,22] Diffuse cortical atrophy, symmetrically increased ventricles, lesions in the white matter with increased T2 signal, and enlarged perivascular spaces may be a normal finding especially with aging. There are descriptions that the left lateral ventricle is usually larger than the right in normal individuals.[21] However, studies have shown that several of these lesions have relation with decreased cognitive function in healthy elderly men.[21,22] Furthermore, in our patient with ventricular asymmetry, there was an important difference from side to side (37%) not expected in normal individuals. Therefore, the abnormalities found in our series of patients with IGE apparently were more frequent and prominent than the normal variance disclosed in healthy individuals.

Previous investigations using volumetry showed that hippocampal atrophy is a reliable marker of hippocampal sclerosis.[23] In an investigation of patients with several forms of epilepsy, only patients with hippocampal sclerosis pathologically proven had atrophy in the MRI evaluation. Among the groups evaluated in this previous analysis, 29 patients with IGE also had normal hippocampal volumes.[23] In another volumetric evaluation of 21 patients with IGE, the authors did not find hippocampal atrophy.[24] Contrary to these reports, the current investigation disclosed reduced hippocampal volumes in 7% (10/134) of patients with IGE. A possible explanation for this finding is the coexistence between partial and generalized epilepsies, a rare condition that should be considered, especially in surgical candidates.[25]

The reduced hippocampal volumes described herein were slightly different from the typical findings of hippocampal sclerosis. Ipsilateral reduction of the fornix is associated with hippocampal atrophy in most of the patients with unilateral hippocampal atrophy.[26] The patients evaluated here did not present reduction of the fornix, and the volumes were reduced bilaterally in half of the patients with hippocampal atrophy. Hippocampal hyperintense T2 signal was present in only one of these patients. Furthermore, there was no correlation between hippocampal volumes and the clinical features.

The pathophysiology of the IGE remains under investigation. Experimental studies suggest that a cortical focus may interact with the thalamus in the generation and maintenance of seizures (cortical focus theory).[27] This theory is also sustained by the presence of focalities in patients with IGE.[28] Nonspecific findings and subtle focal lesions as described in this article may give further support to this theory. Moreover, the MRI abnormalities described here had a congruent localization with the interictal routine EEG in 70% of the patients. The abnormal MRI exams also corresponded to a higher proportion of EEGs with focalities reinforcing the hypothesis that these minor abnormalities may be involved in the clinical and EEG phenotype of IGE.

Interconnections between the thalamus, basal ganglia circuitry, and the cortex are so extensive that the functions of these structures are not consid-

ered separately.[29] The thalamus is involved in the pathophysiology of the major forms of human epilepsy.[2,8,15,30] Because of the extensive number of connections involved in the pathogenesis of partial and generalized epilepsies, including common structures, it is not surprising that partial and generalized epilepsy may coexist.[25] IGEs are a group of complex genetic disorders.[31] IGE phenotypes are not exclusively defined by the genes, but multiple environmental factors also play a role.[32] In some patients, structural abnormalities like the ones described in our study could be involved in the mechanisms of epileptogenicity or influence clinical–EEG phenotype. These abnormalities may act as additional environmental factors influencing the clinical presentation of patients with IGE. Another possibility is that all minor structural abnormalities described may be markers of anomalous circuitries, acquired or inherited, which are possibly involved in the seizure mechanisms of these patients.

The patients in this study were selected in a tertiary epilepsy center reflecting the special condition of the group. All of them presented only generalized seizures (absence, myoclonic, and tonic-clonic) on the clinical evaluation without evidence of focal onset. The abnormalities disclosed by our evaluation did not influence the clinical management of these patients because they were 3 years seizure-free in average under the current therapy at the time of evaluation. However, these MRI findings may stimulate future investigations about antiepileptic drugs in patients with IGE.

Our results also emphasize the importance of the clinical and EEG criteria in the diagnosis of IGE. Following these recommendations, MRI does not need to be routinely performed in patients with typical IGE. However, our findings suggest that, at least in some of these patients, focal abnormalities disclosed by atypical EEG and minor abnormalities on the MRI may have an influence in their clinical presentation. Future studies will be necessary to delineate the implications of these abnormalities in the management of these patients and for better understanding of the pathogenic mechanisms in IGE.

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Voxel-based morphometry in patients with idiopathic generalized epilepsies

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Idiopathic generalized epilepsies (IGE) are a group of frequent age-related epilepsy syndromes. IGE are clinically characterized by generalized tonic–clonic, myoclonic and absence seizures. According to predominant seizure type and age of onset, IGE are divided in subsyndromes: childhood absence and juvenile absence epilepsy (AE), juvenile myoclonic epilepsy (JME) and generalized tonic–clonic seizures on awakening (GTCS). The limits between these subsyndromes are not well defined, supporting the existence of only one major syndrome. Visual assessment of routine magnetic resonance imaging (MRI) in patients with IGE is normal. MRI voxel-based morphometry (VBM) uses automatically segmented gray and white matter for comparisons, eliminating the investigator bias. We used VBM to study 120 individuals (47 controls, 44 with JME, 24 with AE and 15 with GTCS) to investigate the presence of subtle structural abnormalities in IGE subsyndromes. VBM was performed searching for abnormalities on gray matter concentration (GMC) between patients groups and controls. Compared to controls, JME presented increased GMC in frontobasal region and AE showed increased GMC in the superior mesiofrontal region. The GTCS group did not differ from controls. There were no areas of reduced GMC with the statistical level selected. Region of interest analysis showed increased GMC in the anterior portion of the thalamus in patients with absence seizures. Our results support subtle GMC abnormalities in patients with JME and AE when compared to controls. These findings suggest the existence of different patterns of cortical abnormalities in IGE subsyndromes.

Keywords: Epilepsy; Idiopathic generalized epilepsy; MRI; Seizures

Introduction

Idiopathic generalized epilepsies (IGE) are a group of genetically determined epilepsies characterized by generalized tonic clonic, myoclonic and absence seizures (Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), 1989; Janz et al., 1992). According to predominant seizure type and age of onset, IGE are divided in childhood absence epilepsy and juvenile absence epilepsy (AE), juvenile myoclonic epilepsy (JME) and generalized tonic clonic seizures on awakening (GTCS; ILAE, 1989). Despite of the clinical definition, there are frequent overlaps among these subsyndromes, and sometimes their distinction is difficult (Panayiotopoulos, 2002). This clinical overlap was the main argument to support that IGE is a single disease with different phenotypes (Andermann and Berkovic, 2001). On the other hand, genetic studies in a small proportion of patients with clinically homogeneous IGE point to distinct abnormalities among IGE subsyndromes, supporting the existence of different disorders (Zifkin et al., 2005).

The electroencephalogram (EEG) in IGE is strongly supportive when it shows the typical pattern of bilateral, synchronous and symmetrical generalized spike and wave (GSW) or polispike and wave discharges (ILAE, 1989). There are different patterns of abnormalities in the EEG according to the subsyndromes; however, this finding is not constant (Yenjun et al., 2003). Therefore, the EEG sometimes does not help in the distinction of subsyndromes in clinical practice.

Visual assessment of routine magnetic resonance imaging (MRI) in patients with IGEs is usually normal (ILAE, 1989). However, because of the typical clinical and EEG features, MRI is not routinely performed. Quantitative and functional evaluations are increasing the sensitivity of brain MRI. Studies have shown that patients with IGE have subtle abnormalities not identified by routine MRI. These abnormalities are characterized mainly by areas of increased gray matter concentrations (GMC) and metabolic dysfunction in the thalamus and in the frontal lobes

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(Woermann et al., 1999; Mory et al., 2003; Savic et al., 2000). Magnetic resonance spectroscopy also suggests different patterns of abnormality in IGE subsyndromes (Savic et al., 2004).

Voxel-based morphometry (VBM) and the statistical parametric mapping use automatically segmented cerebral gray matter for comparisons. These methods allow comparisons between groups of images and also have other benefits such as reducing the investigator bias (Ashburner and Friston, 2000).

The purpose of this study was to investigate areas of abnormal GMC in three groups of IGE subsyndromes using VBM.

Methods

Subjects

We included 83 consecutive patients with IGE (44 with JME, 24 with AE and 15 with GTCS) from our epilepsy clinic. All patients were re-interviewed with at least one person who witnessed the patient's habitual seizures. Medical records and EEGs were evaluated. Family history was considered positive when at least one first-degree relative had history of seizures. All patients had at least one EEG showing the typical GSW discharges with normal background.

Classification was made according to clinical and EEG features following ILAE recommendations (ILAE, 1989). The control group was composed by 47 normal volunteers (23 women, mean age 32 ± 14, range 19 67). All patients signed an informed consent approved by the Ethics Committee of the UNICAMP Medical School.

MRI scanning protocol

High-resolution MRI was performed using a 2.0 T scanner (Elscint, Haifa, Israel). T1- and T2-weighted images were acquired in axial, coronal, and sagittal planes with thin cuts. In addition, volumetric (3D) T1 gradient echo (GRE) images were acquired in the sagittal plane with 1 mm thick (flip angle = 35°, time to repeat = 22 ms, echo time = 9 ms, matrix = 256 × 220, field of view = 23 × 25 cm). These images were used for VBM analysis. All images were submitted to visual analysis by two independent imaging experts. Patients with abnormalities on the MRI exams were not included in this study.

Image processing

MRI acquisition produces images in DICOM format. All images were converted to ANALYSE format using the software MRIcro (www.mricro.com, Rorden and Brett, 2000). The anterior commissure was selected for the normalization process. Using SPM2 software (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) we normalized, segmented, and smoothed all images (Friston et al., 1995). We also used the optimized VBM code described in previous studies to modulate the images (Good et al., 2001).

In summary, the following steps were carried out:

(i) Spatial normalization: all images were spatially normalized using SPM2 built-in routines, in order to perform the comparisons between groups. This step reduces individual brain size variability by spatially normalizing each image to a template. Normalization used linear and non-linear transformations.

(ii) Segmentation: images underwent automatic segmentation of gray matter using SPM2 built-in routines, which estimate the probability that each voxel is gray matter.

(iii) Modulation: this technique preserves the quantity of tissue that was deformed during the normalization process.

(iv) Smoothing: segmented gray matter images were convolved with an Isotropic Gaussian Kernel of 10 mm to reduce interindividual gyral variation.

Statistical analysis

Comparisons between each one of the IGE groups versus controls were performed. Comparisons between patients with and without valproate in each subsyndrome versus controls were also conducted. This evaluation was performed in order to verify the influence of this medication in our findings. We compared patients who were seizure free for more than 2 years and patients who had seizures in the last 2 years before MRI versus controls.

The statistical analysis for all comparisons was performed with grand mean scaling, proportional threshold masking (0.8) and implicit masking. We defined the contrast searching for areas of reduced and increased GMC. The results were corrected for multiple comparisons using a false discovery rate (FDR) of 1% (Genovese et al., 2002) with an extended threshold looking for clusters with at least of 32 contiguous voxels (Genovese et al., 2002; Bonilla et al., 2004).

Region of interest analysis

The thalamus is traditionally implicated in the pathophysiology of absence seizures and IGE in general (Penfield and Jasper, 1954). To examine this structure, we performed an analysis focused in the medial structures of the brain in patients with absence seizures (23 patients in the JME group and all patients in the AE group) compared to controls and in IGE patients without absence seizures versus controls. A small volume correction was performed placing a sphere with 34-mm radius with its center at coordinates $x = 0, y = -15, z = 1$, involving the thalami bilaterally (Bonilha et al., 2005). Statistical analysis was the same as the previous analysis.

Results

Clinical features

The 83 patients with IGE were divided as follows: JME (n = 44): there were 30 women, mean age was 32 ± 9 years (range 18 63). Mean age of the first seizure was 12 ± 4 (range 2 21). Thirty-two (73%) patients were seizure free for at least 2 years (3 years in average, SD = 2, range 0 10 years). All patients presented myoclonic seizures as the main seizure type, 23 (52%) had absence seizures and 43 (98%) had at least one GTCS in life. At the time of scanning, 33 (75%) patients were taking valproate. Family history was positive in 26 (59%) patients.

AE (n = 24): there were 14 women, mean age was 27 ± 12 years (range 10 62). Mean age of the first seizure was 8 ± 4 (range 1 19). Eighteen (75%) patients were seizure free for at least 2 years (2 years in average, SD = 1, range 0 8). All patients presented absences as the main seizure type, 5 (21%) referred mild myoclonic jerks and 21

(87%) had at least one generalized tonic clonic seizure in life. At the time of scanning, 20 (83%) patients were taking valproate. Family history was positive in 18 (75%) patients.

GTCS (n = 15): there were 8 women, mean age was 29 ± 10 years (range14 51). Mean age of the first seizure was 12 ± 11 (range 1 43). All patients were seizure free for at least 2 years (4 years in average, SD = 2, range 2 11). All patients presented only generalized tonic clonic seizures. At the time of MRI evaluation, 7 (46%) patients were taking carbamazepine and 4 (27%) were taking valproate. Family history was positive in 12 (80%) patients.

Electroencephalographic features

JME-209 EEGs were evaluated: 131 (62%) showed the typical GSW discharges. All patients had at least one EEG with typical GSW discharges. There were 9 (20%) patients with at least one EEG showing focalities (focal or lateralized epileptiform discharges in addition to the typical GSW).

AE-116 EEGs were evaluated: 65 (56%) showed the typical GSW discharges. All patients had at least one EEG with typical GSW discharges. There were 6 (25%) patients with at least one EEG showing focalities.

GTCS-90 EEGs were evaluated: 48 (53%) showed the typical GSW discharges. All patients had at least one EEG with typical GSW discharges. There were 7 (46%) patients with at least one EEG showing focalities.

MRI analysis

JME showed increased GMC in frontobasal regions (coordinates x = ±7, y = 24, z = −18, medial frontal gyrus, Fig. 1A).

AE showed increased GMC in the superior mesiofrontal regions when compared to controls extending from the frontal lobe (coordinates x = ±10, y = −30, z = 67, precentral gyrus) to the parietal lobe (coordinates x = ±10, y = −34, z = 67, postcentral gyrus, Fig. 1B).

There were no differences in GMC in the comparison between GTCS and controls. There were no areas of decreased GMC with the statistical level selected for all subsyndromes in comparison to controls.

Comparisons between patients with and without valproate and comparisons between patients who were seizure free for more than 2 years and patients who had seizures in the last 2 years in each subsyndrome versus controls showed results similar to the evaluation including all patients in each subgroups. Comparison between patients who were seizure free for more than 2 years and patients who had seizures in the last 2 years before MRI versus controls was not performed for GTCS patients because all of them were more than 2 years seizure free.

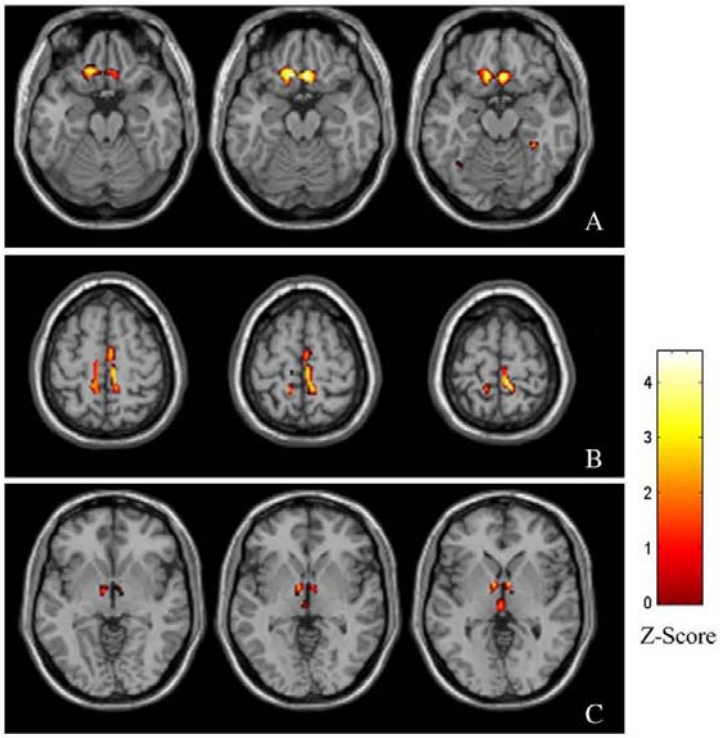

Fig. 1. Results of the voxel-based morphometry analysis comparing patients with JME (A) and AE (B) versus 47 healthy controls, showing areas of increased GMC located in the frontobasal (A) and superior mesiofrontal regions (B). Panel C shows a region of interest comparison between patients with absence seizures (23 JME and 24 AE) and controls, showing areas of increased GMC mainly at the anterior portion of both thalami. The results of these comparisons are displayed as a statistic parametric map of the t statistic ($SPM_{(t)}$). This figure illustrates the results superimposed in multislice coronal T1 template images of a normal brain. The colorbar indicates the number of standard deviations compared to controls (z score). The level of significance selected was a $P < 0.05$ corrected for multiple comparisons (false discovery rate).

Region of interest analysis of the thalami

Group comparisons with controls showed small areas of increased GMC which were more pronounced in the anterior portions of thalami in patients with absence seizures (coordinates $x = \pm 9$, $y = -8$, $z = 0$, Fig. 1C) but not in patients without absence seizures. There were no areas of decreased GMC with the statistical level selected.

Discussion

After the description of the minimal malformations of cortical development described by Meencke and Janz (1984) in patients with JME, there have been a growing number of studies trying to investigate MRI abnormalities. Descriptions of patients with MRI evidence of periventricular nodular heterotopias with clinical presentation resembling IGE also raised the question of structural abnormalities as a possible pathophysiological mechanism for IGE (Raymond et al., 1994; Dubeau et al., 1995). However, a large study with IGE patients has not been performed and these findings, as the description of the pathological studies, remain controversial (Lyon and Gastaut, 1985).

VBM technique was previously validated and has been used for the investigation of partial epilepsies (Good et al., 2001; Bonilla et al., 2004, 2005). A former study using VBM in IGE evaluated a group of 20 patients with JME (Woermann et al., 1999). The authors found an area of increased GMC located at the mesial frontal lobes. Our study was unable to find such an extensive area. Comparison of patients with JME and controls showed a bilateral frontobasal region of increased GMC. Possible explanations for this divergence are the differences in the images processing, clinical features and the number of patients studied.

The group with AE showed a different pattern of increased GMC from the other comparisons. A predominantly superior mesiofrontal alteration was observed. This difference probably is related to the fact that absence was the main seizure type in this group of patients. This observation suggests that there are different mechanisms for the pathogenesis of each IGE subsyndrome.

Valproate may cause reversible pseudoatrophy of the brain (Guerrini et al., 1998). The clinical presentation is characterized by cognitive declined associated with cortical atrophy on neuroimaging. The symptoms usually initiate after the introduction of the medication and may have a quick or insidious progression. After discontinuation of the medication, the clinical symptoms and the neuroimage findings usually disappear (Guerrini et al., 1998). The patients investigated in this study that were under valproate therapy did not present the clinical features resembling cerebral pseudoatrophy. Nevertheless, since the therapy was not uniform in the patients evaluated, there is a possibility that the medication influenced in our findings. This hypothesis probably was not confirmed here because there were no differences between patients with and without valproate. Furthermore, increased areas of GMC disclosed by our results are exactly the opposite of the finding expected in patients taking valproate. Our results probably were not influenced by seizure control since the findings were not different for patients with more than 2 years seizure free and patients who had seizures within the 2 years prior to MRI scan. Since all patients were under medication and had very few seizures over the last several years, it is difficult to evaluate the real influence of seizure frequency in this series. However, the findings of increase GMC is in opposite direction to what one would expect based on clinical and experimental data about seizure frequency and neuronal damage.

The thalamus is considered one of the main structures involved in the IGE pathophysiology. Experimental studies showed that the thalamus is involved in the generation of the GSW discharges and absence seizures (Meeren et al., 2002). A similar mechanism also may be responsible for myoclonic seizures (Avanzini et al., 2000). Region of interest VBM analysis showed increased GMC located in the anterior portion of the thalamus in patients who presented absence seizures (23 JME and 24 AE). The anterior portion of the thalamus is composed mainly by the thalamic reticular nucleus. This nucleus is directly implicated in the GSW pathophysiology (Slaght et al., 2002). Our findings suggest a structural abnormality, characterized by increased GMC in the anterior portion of the thalamus. These results are in agreement with manual segmentation of thalami in the same population of patients (Betting et al., in press). However, previous studies using quantitative MRI failed to demonstrate structural abnormalities in the thalamus of patients with IGE (Natsume et al., 2003; Seeck et al., 2005). Comparison between the manually segmented thalamic volumes of 17 patients with IGE and controls showed no differences (Natsume et al., 2003). Another study evaluating the caudate nucleus, putamen, pallidum and the thalamus of 11 patients with various IGE syndrome compared to15 age-matched controls also was unable to find differences between the thalamic volumes (Seeck et al., 2005). The larger number of patients evaluated and differences in acquisition and processing of the images may explain our different findings.

The results described above may represent the circuitry involved in IGE seizure generation. EEG findings remain controversial about the real site of initial epileptiform discharges in patients with IGE (Velasco et al., 1989; Meeren et al., 2002). Experimental models of absence seizures are evidencing that probably there is an underlying focal abnormality that is responsible for the onset of the GSW discharges. The thalamus would be secondarily affected in this model (Meeren et al., 2002). The focal abnormalities described in the present study are in agreement with this theory.

Using a semi-automatic segmentation technique, a previous work found increased gray matter volumes in patients with IGE including GTCS (Woermann et al., 1998). However, this study was not designed to determine the exact location of volume increase. Despite of this, we were unable to find GMC differences in GTCS patients compared to controls. The small number of patients in our group of GTCS probably limited the statistical power of the analysis.

The microscopic and electrophysiological correlates of these areas of increased GMC are unknown; however, axonal and dendritic arborization, in addition to neuronal size and number, may be important contributors to the density of gray matter observed in MRI (Mechelli et al., 2005). Interestingly, the finding of areas of increased GMC in patients with IGE is in contrast to VBM results in patients with temporal lobe epilepsy (Bonilla et al., 2004, 2005).

The mechanism underlying the clinical and EEG focalities in IGE is poorly understood (Leutmezer et al., 2002). The present study gives support for the presence of minor structural cortical and subcortical abnormalities in patients with JME and AE. It is possible that these abnormalities, if confirmed in subsequent studies, could explain, at least in part, the presence of clinical and EEG focalities. In addition, our study showed that there are

different patterns of increased GMC in the three main IGE subsyndromes. These differences in subtle structural abnormalities could be related to the clinical and genetic peculiarities in IGE subsyndromes.

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Investigation of focalities in idiopathic generalized epilepsies using voxel-based morphometry

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Abstract

Purpose: EEG is supportive of idiopathic generalized epilepsies (IGE) diagnosis when it shows typical generalized spike and wave (GSW) discharges with normal background. Despite of this feature, sometimes focal epileptiform discharges may be registered in the EEG. Voxel-based morphometry (VBM) is a quantitative technique of MRI analysis which increases the sensibility to detect small areas of structural abnormalities. The objective of this study was to investigate the focalities present in the EEG of patients with IGE using VBM.

Methods: All patients had at least one EEG with typical GSW discharges and one with clear focal epileptiform discharges. A volumetric MRI sequence was used for VBM analysis. After processing, images of each patient were individually compared with a group of 47 controls. Statistical analysis was performed searching for areas of gray matter concentration (GMC) abnormalities. The localization of the focal discharges on the EEG was compared to the VBM results.

Results: Twenty-two patients with IGE diagnosis were evaluated. Nine patients had juvenile myoclonic epilepsy, 89% presented areas of GMC abnormalities and 75% presented correspondence with the EEG focalities. Six patients had absence epilepsy, 83% presented areas of GMC abnormalities and 60% presented correspondence with the EEG focalities. Seven had generalized tonic-clonic seizures on awakening, 71% presented areas of GMC abnormalities and 40% presented correspondence with the EEG focalities.

Conclusion: This study supports that subtle structural abnormalities characterized mainly by increased GMC may be associated with focal epileptiform discharges observed in the EEG of IGE.

Introduction

Idiopathic generalized epilepsies (IGE) are a group of epilepsies characterized by generalized onset of the seizures. Generalized tonic-clonic, absence and myoclonic seizures may be present. According to the predominant type of seizure and the age of onset IGE are divided in subsyndromes [Commission on Classification and Terminology of the International League Against Epilepsy, ILAE, 1989]. The main subsyndromes with onset in childhood and adolescence are childhood absence epilepsy, juvenile myoclonic epilepsy (JME), juvenile absence epilepsy and generalized tonic clonic seizures on awakening (GTCS) [ILAE, 1989; Panayiotopoulos, 2002].

The inter-ictal electroencephalogram (EEG) is very supportive of IGE diagnosis when it shows the typical generalized spike and wave (GSW) discharges with normal background [Panayiotopoulos, 2002]. Despite of this, focalities may be present from 8 to 55% of the inter-ictal records of JME patients [Waltz, 2000]. The pathophysiology of the GSW involves an extensive network and mainly the thalamo-cortical circuitry. Despite of the hypothesis of a diffuse cortical hyperexcitability involved in the onset of the generalized seizures, experimental studies suggests that generalized seizures have a focal background [Gloor, 1968; Meeren et al., 2002].

There are several hypotheses involving the focalities sometimes disclosed in the EEG records of patients with IGE. These focalities may represent fragmented generalized discharges or may reflect focal cortical pathology. Another possible explanation is a localized self-sustaining hyperexcitability [Lombroso, 1997]. Therefore, the underlying mechanism involving these focal discharges are currently under debate. A better comprehension of the meaning and etiology of the focalities present in the EEG of patients with IGE may help to understand the pathophysiological mechanisms of these diseases.

Quantitative techniques of magnetic resonance imaging (MRI) analysis are increasing the detection of subtle structural abnormalities in patients with IGE [Woermann et al., 1999]. Voxel-based morphometry (VBM) is a method which allows the comparison between MRI images. This method uses automatic segmented gray matter for the comparisons [Ashburner and Friston, 2000]. The objective of this study was to investigate the relationship between focalities present on the EEG records and focal changes in gray matter concentration using VBM in patients with IGE.

Methods

Subjects: Twenty-two consecutive patients with IGE diagnosis were selected. Patients were classified in three groups: JME, GTCS and absence epilepsy (AE) which included childhood absence epilepsy and juvenile absence epilepsy. Classification was performed according to clinical and EEG criteria [ILAE, 1989; Panayiotopoulos, 2002]. All patients and one person who previously watched a typical seizure were re-interviewed. Medical records were also analyzed. Patients that not met the criteria or with suspected partial epilepsy were excluded of the study.

EEG recording protocol: All EEGs were performed in inter-ictal state. A 16 or 32 channel EEG recorder and the international 10-20 electrode placement were used. The recording was made according to previous recommendations including 20 minutes at least, three different montages, hyperventilation and photic stimulation. All patients presented at least one EEG with the typical GSW discharges with normal background. Patients included also had a minimum of one record with a clear focal or generalized asymmetrical epileptiform discharge. Slow waves were not considered as focality. Persistence of focalities was defined as the time between the first and the last record with focalities.

MRI acquisition protocol: Images were acquired in a 2T (GE Elscint, Haifa, Israel) scanner. Volumetric (3D) T1 GRE was acquired in the sagital plane with 1mm thick (flip angle=35°, TR=22, TE=9, matrix=256 x 220, FOV=23 x 25cm). This sequence was used for VBM analysis.

Image processing: The images acquired were in DICOM format. MRIcro software (www.mricro.com) was used to transform images into ANALYZE format allowing the further steps. SPM2 software (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) was used for image processing and statistical analysis. Based on the anterior commissure, all images underwent spatial normalization. The normalization reduces the interindividual variation of the brain size. Linear and non-linear transformations were used for normalization. Normalized images were then submitted to an optimized VBM protocol as previously described

[Good et al., 2001]. This protocol included automatic segmentation of the cerebrospinal fluid, white and gray matter. After that, images were modulated. Modulation preserves the tissue that was eventually deformed in the normalization protocol. The final step consisted in smoothing of the images convolving them with an Isotropic Gaussian Kernel of 10mm to reduce interindividual gyral variation.

Statistical analysis: The MRI image of each patient was individually compared to a control group of 47 healthy volunteers (23 women, mean age 32 ± 14, range 19-67). Comparisons were performed searching for areas of increased gray matter concentration (GMC) and areas of gray matter atrophy. Each evaluation included grand mean scaling, proportional threshold masking (0.8) and implicit masking. Threshold selected was a $p<0.05$ corrected for multiple comparisons (false discovery rate) with an extended threshold looking for clusters with at least of 32 contiguous voxels.

Results

Nine patients had JME (3 women, mean age 29 years ± 7, range 20-41), Six of these patients presented myoclonic, absence and generalized tonic-clonic seizures, two presented myoclonic and generalized tonic-clonic seizures and one presented myoclonic and absence seizures. Focal semiology suggestive of auras or partial complex seizures was described in four (44%) patients (tables 1 and 2).

Six patients had AE (5 women, 21 mean age years ± 13, range 11-47), five of these patients presented absence and rare generalized tonic-clonic seizures and one presented absence seizures only. Focal semiology suggestive of auras or partial complex seizures was described in 1 (16%) patient (tables 1 and 2).

Seven patients had GTCS (4 women, mean age 28 years ± 9, range 20-48). Two patients presented myoclonic and generalized tonic-clonic seizures, one had absence and generalized tonic-clonic seizures and four had generalized tonic-clonic seizures only. Focal semiology suggestive of auras or partial complex seizures was described in 3 (43%) patients (table 1 and 2).

One hundred and twenty nine EEG records were re-evaluated. There was a mean of 6 ± 3 EEG records performed for each patient (range 1-12). There was 52 EEG exams performed in the JME group (28, 54% with focalities), the persistence of focalities (defined as the presence of focality in the same location in two distinct EEG records regardless of the time interval between then) ranged from 7 months to 18 years (in two patients they were present in only one record). The location of the focalities was the same in 7 patients. There were 31 EEG exams performed in the AE group (8, 26% with focalities), the persistence of focalities ranged from 2 to 3 years (in four patients they were present in only one record). The location of the focalities was the same in two patients. There was 46 EEG exams performed in the GTCS group (26, 56% with focalities), the persistence of focalities ranged from 7 months to 9 years. All patients presented at least two EEG records with focalities in the same region. Tables 2 and 3 abridge these findings.

All MRI images were submitted to visual analysis and no significative abnormalities were described.

VBM comparisons showed areas of GMC abnormalities in 18 of 22 (82%) patients evaluated. Nine of the 18 (50%) patients showed only areas of increased GMC, three (16%) showed only gray matter atrophy and 6 (34%) showed both the presence of increased and atrophy of the gray matter concentration.

All patients (8) with focal description on the semiology had abnormalities on the VBM analysis. Eleven (10 increased GMC and one gray matter atrophy) of the 18 patients (61%) had correspondence between EEG and the VBM analysis. Four of 8 patients with focal semiology (50%) had correspondence between the clinical description, EEG and VBM analysis.

Juvenile myoclonic epilepsy: Eight of the 9 (89%) patients presented areas of abnormal GMC. EEG analysis showed concordance of the region in 6 of 8 patients (75%). The areas of abnormal GMC with EEG concordance were located at the frontal lobe in four patients. In two patients they were located in the right anterior portion of the frontal lobe (figure 1A and 1B), in one patient in both frontal lobes with left predominance (figure 1D) and in one patient in the left frontal lobe (figure 1E). In one patient the area of

increased GMC was located in both insula with right sided predominance (figure 1C) and in one patient in the left temporal lobe (figure 1F).

Absence epilepsy: Five of the 6 (83%) patients presented areas of abnormal GMC (figure 2). EEG analysis showed concordance of the region in 3 of 5 patients (60%). The areas of abnormal GMC with EEG concordance were in the frontal lobe in two patients (one right and one left, figures 2A and 2B) and at the right insula in one patient (figure 2C).

Generalized tonic-clonic seizures: Five of 7 (71%) patients presented areas of abnormal GMC (figure 3). EEG analysis showed concordance of the region in 2 of 5 patients (40%). The areas of abnormal GMC with EEG concordance were located at the superior portion of the right temporal lobe (only this patient presented the concordance among semiology, EEG and gray matter atrophy; figure 3A) and at the left insula (figure 3B).

Table 1, 2 and 3 summarizes the data presented above.

Discussion

MRI scan is not routinely performed in patients with clinical diagnosis of IGE. The clinical and EEG features when typically present are very supportive of the diagnosis and no additional investigation is recommended [King et al., 1998]. On the other hand, focal epilepsies are more clearly associated with structural lesions. In theory, the limits between these epileptic syndromes appears to be very clear however, in the daily practice sometimes the distinction is difficult. The present study showed that 82% of patients with IGE and focalities on the EEG may have an area of structural abnormality using VBM analysis. These findings supports that small areas of cortical abnormalities may be responsible for IGE mechanisms. Clinical variability may be associated with the location of the cortical abnormality, genetic predisposition and environmental factors influencing the brain. This multifactorial mechanism is in accordance with genetic studies which failed to point a single gene for the IGE [Delgado-Escueta et al., 1999].

There are no studies using VBM technique in the evaluation of patients with IGE with clinical and EEG focalities. A previous study using VBM showed 25% (5/20) of JME patients with areas of gray matter abnormalities [Woermann et al., 1999]. Two patients presented areas of increased GMC and three patient areas of decreased GMC. Despite of the higher number of patients with GMC atrophy, the group comparison showed increased GMC [Woermann et al., 1999]. The rate of abnormalities described in the present study for JME patients was higher (89%). This difference is probably due to a more powerful MRI scanner and the distinct protocol in images acquisition and processing. Furthermore, all patients evaluated in this study had at least one EEG with GSW and focal discharges.

JME showed a higher percentage of patients with focalities on the VBM analysis than AE and GTCS (89%, 83% and 71%). These findings supports that, at least in part, the focalities on the EEG of patients with IGE are related to a focal structural lesion. Moreover, the focalities on EEG are predominantly related with areas of increased GMC. Only one patient with GTCS showed area of gray matter atrophy corresponding to EEG and VBM evaluations. Visual analysis did not revealed abnormalities in these patients. Therefore, VBM may be a useful tool selecting uniform groups of patients for studies, including genetic analysis.

This study evaluated only well consistent focal epileptiform discharges. There are descriptions of up to 56% of focalities with constant location in time [Lombroso, 1997]. All patients examined in the present analysis persisted with the focalities in constant or close location even after 18 years. The total number of EEG focalities was higher in patients in the GTCS group (56%) than the JME and AE groups (54% and 26% respectively). Even with the higher rate of focalities in the total number of EEG performed, GTCS group had the lowest number of patients with structural abnormalities when individually compared to controls (71%). On the other hand, AE showed a lower number of focalities in the total number of EEG performed (26%) and a higher percentage of abnormalities in the VBM analysis (83%). The possible explanation to this difference between patients with AE and GTCS is some EEG data bias. The population studied was in a tertiary center and all the patients were referred. In the presence of

focalities in the clinical evaluation and on the EEG, as well as unusual treatment response IGE diagnosis should be reviewed. Patients with GTCS and focalities were probably conducted as having focal epilepsy. This is supported by the medications (only one patient was taking valproate). This bias was probably caused by the higher number of patients with only one record in AE group and some patients that were submitted to multiple exams showing the same finding in GTCS group. IGE diagnosis in patients with GTCS may be difficult especially in late onset of the seizures and long lasting epilepsies. The whole clinical picture including a detailed clinical history, EEG and MRI have to be evaluated for a correct diagnosis. The patients in GTCS group studied here have important characteristics suggesting IGE diagnosis: normal MRI at visual analysis, EEG with GSW discharges, excellent drug response (5 years seizure free in average) and strong family history (6 of the 7 patients).

In more than a half of the cases evaluated, the focal EEG had concordance with MRI showing the same location (61%). For patients with JME this congruence was higher (75% JME, AE 60% and GTCS 40%). Despite of the small number of subjects evaluated, this finding may suggest a different mechanism for each IGE subsyndrome. All subsyndromes may present with all seizure types. The differentiation is made based in the predominant seizure type and age of onset [ILAE, 1989; Panayiotopoulos, 2002]. In the GTCS group, only four patients presented exclusively generalized tonic-clonic seizures. Two of than does not presented abnormalities on VBM analysis and none presented congruence between EEG and VBM. Therefore, the findings reported in this group may be related to the presence of other seizure types. This is probably explained because the pathophysiology of the absence and myoclonic seizures are more similar than the mechanism of generalized tonic-clonic seizures. Absence and myoclonic seizures in IGE patients involve mainly the thalamo-cortical circuitry and the findings described may reflect the involvement of the cortex in this mechanism [Meeren et al., 2003; Avanzini et al., 2000]. According to experimental studies, myoclonic and especially absence seizures may have a focal onset in the cortex [Meeren et al., 2002]. The discharge rapidly spreads and involves the thalamus. The interaction between thalamus and cortex is responsible for the maintenance of the seizure [Meeren et al., 2002]. The pathophysiology of the generalized tonic-clonic seizures is related with ascending impulses of the brainstem

[Browning, 1994]. This difference may also be related with the smaller frequency of focal discharges reported in patients with GTCS (2.6%) compared to patients with JME (36.7%) [Janz, 2000; Aliberti et al., 1994].

The focal semiology was is agreement with EEG and MRI in only 50% of the patients. However, this rate probably is underestimated because video-EEG monitoring was not performed. The description of focal semiology was collected in routine evaluations and during the inter-ictal EEG. Video-EEG monitoring provides more detailed and trustable data and this method is very useful helping to establish the correct diagnosis and appropriate treatment. Using video-EEG, clinical and EEG focalities were reported in 54% of patients with JME [Usui et al., 2005]. Additionally, auras were also reported in patients with IGE occurring in as much as 70% of monitored patients [Boylan et al., 2006]. Despite of this, all patients investigated here with clinical description of focalities had abnormalities on VBM analysis. These findings suggest that detailed clinical history is important and may give clues of the quantitative analysis results.

The cortical areas of increased gray matter detected by the morphometric analysis may correspond to structural abnormalities such as displasia. This finding would be in agreement with the previous descriptions of anathomopathological abnormalities in patients with JME [Meencke and Janz, 1984]. Another possible explanation, is that these areas may represent changes in neuronal connectivity [Woermann et al., 1999]. These changes are more closely related with neuronal function and are also supported by reports of reduced concentrations of N-acetyl-aspartate in the frontal lobe of patients with JME revealed by MRI spectroscopy [Savic et al., 2000]. Therefore, the results described suggest that in the clinically heterogeneous patients with IGE part of than present cortical abnormalities on MRI. These cortical abnormalities are possibly involved in the pathogenesis of the focal features present in some patients with IGE.

The areas of abnormal GMC described here, may influence clinical and EEG presentation of the focalities. Nevertheless, further studies are needed to clarify the relation of these areas with the pathophysiology of the IGE. There are studies showing that in a few number of patients generalized and partial epilepsies may coexist [Diehl et al., 1998]. However, in the group evaluated here this possibility is undermined by the high rate of

patients presenting areas of abnormal GMC (82% of IGE patients). This number of patients presenting both partial and epilepsy is very unlikely. Furthermore, most of the patients had a good seizure control with 3 years of seizure free in average. The absence of description of other seizure types than the generalized also supports that the patients studied did not present coexistence between partial and generalized epilepsies.

Focal epilepsies occasionally may have generalized discharges on the EEG as a result of a secondary bisynchrony [Tükel and Jasper, 1952]. This finding may lead to an erroneous diagnosis of IGE. The results presented here supports that at least part of the IGE may have focalities on the investigation confirmed by clinical, EEG and quantitative MRI investigation. In these situations, the exact classification of the patients is difficult. Basically, classifications try to group common diseases in order to facilitate the clinical practice, teaching and research. It must be remembered that, in some cases as presented here, the whole clinical, EEG and MRI picture may reveal intermediary situations.

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Tables

Table 1- Clinical features of 22 consecutive patients with idiopathic generalized epilepsy. Patients 1, 8, 13 and 14 does not presented area of abnormalities in the individual MRI voxel-based morphometry analysis compared to controls.

Pat.	Family history	Age*	Onset* sz	Last* sz	Gender	Seizure type	AED	Syndrome
1	Two brothers, mother	31	17	2	M	M, A, G	VPA	JME
2	Negative	22	4	3	W	A, G	CBZ	CAE
3	Two brothers	24	12	5	W	M, A, G	VPA	JME
4	Sister, father	20	7	3	M	M, G	VPA	JME
5	Negative	32	12	0	M	M, G	VPA	JME
6	Mother's uncles	29	16	0	M	M, A, G	VPA	JME
7	Negative	23	6	5	M	M, A, G	VPA	JME
8	Uncle	19	10	1	W	A, G	VPA	JAE
9	Negative	27	2	2	W	M, A, G	VPA	JME
10	Four cousins	39	15	2	M	M, A	VPA	JME
11	Brother, father	25	3	4	W	G	CBZ	GTCS
12	Brothers, cousins	22	3	11	W	A, G	None	GTCS
13	Uncle, cousin	35	11	2	M	G	CBZ	GTCS
14	Sister, father	27	3	8	M	G	DPH	GTCS
15	Uncle	20	7	2	W	M, G	CBZ	GTCS
16	Mother, brother	48	43	4	W	M, G	CBZ	GTCS
17	Uncle	12	8	2	W	A, G	VPA	CAE
18	Grandmother	11	2	0	W	A	ETX	CAE
19	Negative	23	1	6	M	G	VPA	GTCS
20	Brother	41	7	5	W	M, A, G	VPA	JME
21	Brother, cousin and uncle	47	7	2	W	A, G	VPA	JAE
22	Negative	17	10	3	M	AG	VPA	JAE

Legend: Pat.-patient, M-man, W-Woman, M-myoclonic, A-absence, G-generalized tonic-clonic seizures, AED-antiepileptic drug, VPA-valproate, CBZ-carbamazepine, DPH-phenytoin, ETX-ethossuximide, JME-juvenile myoclonic epilepsy, CAE-childhood absence epilepsy, JAE-juvenile absence epilepsy, GTCS-generalized tonic-clonic seizures on awakening, sz-seizure, [*]-expressed in years.

Table 2- Focal features of 11 patients with idiopathic generalized epilepsy disclosed by semiology, EEG and magnetic resonance imaging / voxel-based morphometry (VBM). VBM analysis was performed searching for gray matter concentration abnormalities. Statistical level selected was $p < 0.05$ corrected for multiple comparisons (false discovery rate).

Pat.	Semiology	EEG	MRI/VBM
2	Focalities not described	Independent bilateral parieto-temporal spikes and sharp waves	Right insula and right frontal lobe
3	Focalities not described	Independent bilateral frontal spikes	Bilateral frontal lobe (left predominance)
4	Mouth deviation	Independent bilateral fronto-temporal spikes	Right frontal lobe
7	Extension of the left arm	Synchronous and independent frontal-temporal spikes (left predominance)	Left frontal
9	Focalities not described	Generalized spikes with right fronto-temporal predominance	Insula bilateral (right predominance)
10	Myoclonic jerks on the right superior arm	Generalized spikes with bilateral fronto-temporal predominance	Left temporal
12	Head deviation for the left	Bilateral independent fronto-temporal spikes	Right fronto-temporal*
16	Myoclonic jerks on the left hand	Left fronto-temporal sharp waves and spikes	Left insula
17	Focalities not described	Generalized spikes with right fronto-temporal predominance	Right frontal lobe
18	Focalities not described	Left centro-temporal sharp waves	Left frontal lobe
20	Myoclonic jerks on the right superior arm	Generalized and isolated spikes with bilateral independent fronto-temporal predominance	Right frontal lobe

* Area of gray matter concentration atrophy

Table 3- General features of the EEG focalities observed in twenty-two patients with idiopathic generalized epilepsy.

	JME	**AE**	**GTCS**	**Total**
Total of EEGs performed (n)	52	31	46	129
Focalities	28 (54%)	8 (26%)	26 (56%)	62 (48%)
Persistence of location*	7 patients	2 patients	7 patients	16 patients

* Defined as the presence of focality in the same location in two distinct EEG records regardless of the time interval between then.

Legend: JME-juvenile myoclonic epilepsy, AE-absence epilepsy, GTCS-generalized tonic-clonic seizures on awakening.

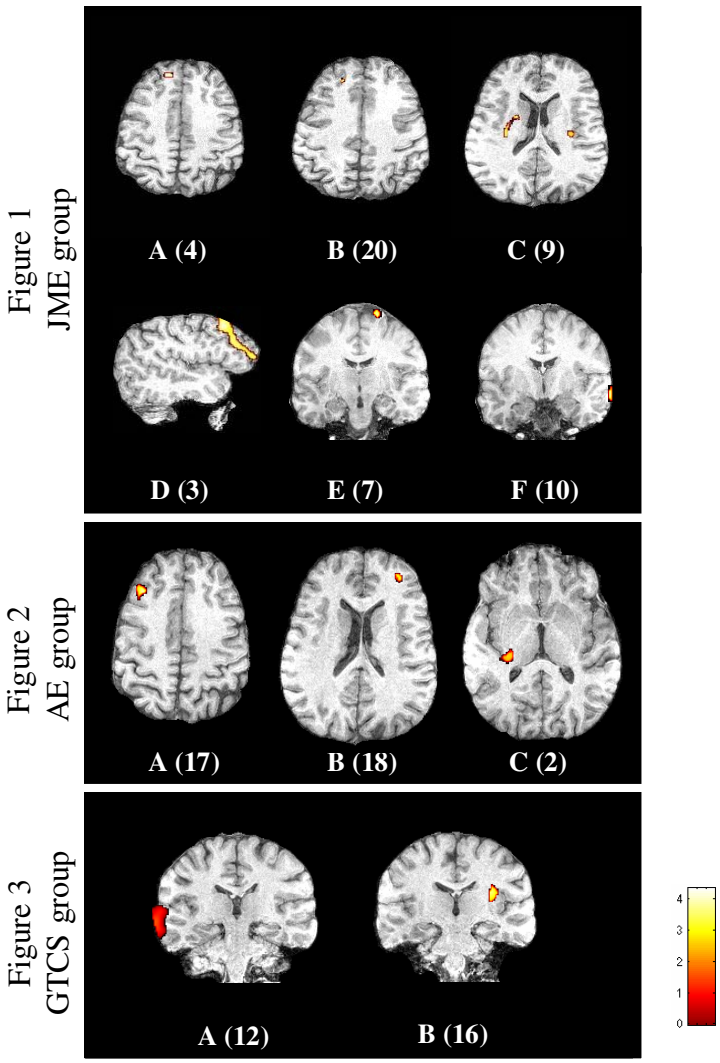

Figure 1-3- Results of the comparison between patients with juvenile myoclonic epilepsy (JME, figure 1), absence epilepsy (AE, figure 2) and generalized-tonic clonic seizures on awakening (GTCS, figure 3) individually with 47 controls searching for areas of gray matter concentration abnormalities. In these patients the areas of cotical abnormalities were in agreement with the EEG. Patient number is in parenthesis. The results (color areas) are superimposed with an anatomical template. The color represents the number of standard deviations compared to controls as indicated by the scale on the right inferior portion of the figure. Each slice represents one patient compared with controls. Statistical analysis was performed with a corrected $p < 0.05$ (false discovery rate). Only patient number 12 (figure 3A) presented area of gray matter atrophy.

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MRI volumetry shows increased anterior thalamic volumes in patients with absence seizures

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Abstract

The interaction between thalamus and cortex appears to be critical to the pathophysiology of idiopathic generalized epilepsies (IGEs). The objective of this study was to investigate thalamic volumes of a group of patients with IGEs using high-resolution MRI. Thalamic segmentation was performed by the same rater, who was unaware of the diagnosis. Thalamic volumes were divided into anterior half and posterior half. One hundred forty-seven patients were scanned (71 with juvenile myoclonic epilepsy, 49 with generalized tonic–clonic seizures only, and 27 with absence epilepsy). Subgroup analyses with corrections for multiple comparisons showed that, when compared with those of controls, anterior thalamic volumes were increased in patients with absence epilepsy and juvenile myoclonic epilepsy with absence seizures, but not in patients with generalized tonic–clonic seizures only and juvenile myoclonic epilepsy without absence seizures. Our results demonstrated that the anterior thalamus is structurally different in patients with IGEs and absence seizures as compared with patients with IGEs without absence seizures.

Keywords: Idiopathic generalized epilepsies; Magnetic resonance imaging; Volumetry; Thalamus; Absence seizures; Juvenile myoclonic epilepsy

1. Introduction

Magnetic resonance imaging (MRI) is normal in patients with idiopathic generalized epilepsies (IGEs). These age-related epilepsies have a genetic background, and no underlying neuropathological finding is expected [1]. The description of minimal cortical malformations in patients with IGEs raised the possibility of structural abnormalities as a mechanism of seizure generation [2].

According to the initial hypothesis for the pathophysiology of absence seizures and the IGEs, known as the centrencephalic hypothesis, midline subcortical structures are capable of ictal engagement of both cerebral hemispheres [3]. This hypothesis was attractive because it explained the bisymmetrical and bisynchronous onset of the seizures revealed by the EEG findings. Since this description, the thalamus has been a key structure in studies of IGEs.

Experimental data point to involvement of the thalamocortical circuitry in the generation of spike and wave discharges (SWDs) in patients with IGEs [4]. Models of generalized absence seizures suggest that the thalamus is critical to the maintenance of the discharges [4,5]. Despite this, anatomical investigations in animals did not disclose any relevant structural findings [6].

MRI spectroscopy reveals a thalamic dysfunction in patients with different IGE subsyndromes including juvenile myoclonic epilepsy (JME) and in patients with generalized tonic–clonic seizures [7–9]. These findings support the presence of a thalamic functional abnormality not only in absence seizures but in all IGE subsyndromes. Previous studies were unable to find any difference in thalamic volumes between patients with IGEs and controls [9–11].

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The real contribution of the thalamus to seizure onset and clinical variability is under investigation, and the pathophysiology of the IGEs is not completely understood. High-resolution MRI allows precise anatomical evaluation in vivo. The objective of this study was to examine the thalamic volumes of a large group of patients with IGE subsyndromes using high-resolution MRI and to compare the findings with those for a healthy control group.

2. Methods

2.1. Subjects

MRI was performed in 147 consecutive patients (90 women, mean age = 32 ± 12 (±SD), range = 10 79) and 45 healthy volunteers (22 women, mean age = 32 ± 13, range = 20 60). To investigate thalamic structure in different seizure types (generalized tonic clonic, absence, and myoclonic), patients were divided into three subsyndromes: 71 had JME (46 women, mean age = 32 ± 9, range = 15 63), 49 had generalized tonic clonic seizures only (GTCSs, 27 women, mean age = 36 ± 14, range = 14 79), and 27 had absence epilepsy (AE, 17 women, mean age = 27 ± 12, range = 10 62).

The classification was performed following ILAE recommendations [1]. Subsyndromes were differentiated according to the main seizure type at the time of MRI acquisition. Seizures were classified on the basis of a detailed clinical history taken from all patients and at least one person who previously observed a typical seizure. IGE diagnosis was also based on the entire clinical context, such as the presence of appropriate drug response, seizure recurrence after antiepileptic drug (AED) withdrawal, relationship of the seizures to the sleep wake cycle, positive family history, and triggering factors. Patients with suspected focal onset of the seizures were excluded.

2.2. Electroencephalography

All patients were submitted to at least one 20- to 30-minute interictal electroencephalographic examination with hyperventilation and intermittent photic stimulation using a 16- or 32-channel EEG recorder. Most of them had several EEG recordings (mean = 4 ± 3, range = 1 15). We used the International 10 20 System for electrode placement. Sleep deprivation was not used.

2.3. Magnetic resonance imaging

All images were acquired in a 2.0-T scanner (Elscint Prestige). The volumetric three-dimensional T1 gradient echo sequence with 1-mm isotropic voxels was used for volumetry (flip angle = 35°, repetition time = 22 ms, echo time = 9 ms, matrix = 256 × 220, field of view = 230 × 250 mm). The software Display (developed by the Brain Imaging Center; Montreal Neurological Institute; Montreal, Quebec, Canada) was used for thalamic segmentation. Images were previously processed for field nonhomogeneity correction and intensity standardization. This correction produces more consistent relative gray matter, white matter, and cerebral spinal fluid intensities [12]. Images were then submitted to linear stereotaxic transformation into a standard space [13]. This processing adjusts the images for differences in total brain volume, allowing analysis between individuals. Stereotaxic transformation also adjusts brain orientation, facilitating the identification of anatomic boundaries [14]. Anatomic landmarks for thalamic delineation were adopted according to previous publications (Fig. 1) [9,10]. All measures were performed by the same person after a training period. Volumes are expressed in cubic millimeters.

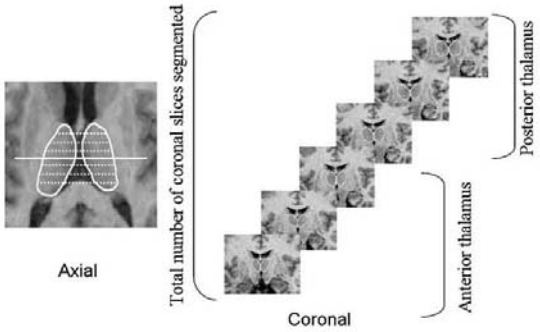

Fig. 2. Schematic example of division of the thalamus into anterior and posterior portions. According to the total number of slices segmented (six in this example), we divided the thalamus into anterior and posterior halves (three slices were included in the anterior thalamic volumes and three in the posterior thalamic volumes).

The major part of the anterior thalamus in mammals is the thalamic reticular nucleus [15]. Animal studies indicate that the anterior thalamic nuclei are involved in generalized SWDs [16,17]. To investigate volume abnormalities in this region, the thalamus was divided into anterior and posterior according to the total number of coronal slices segmented (Fig. 2).

The observer was not aware of the subject's diagnosis. The intrarater reliability in thalamic volume measurement was 1.4 ± 5.6% in the left and 1.1 ± 6.1% in the right thalamus in 34 normal controls, with measurements performed 3 months apart.

2.4. Statistical analysis

We used the average of the right and left thalamic volumes to simplify statistical analysis, as there was no side-to-side difference in patients and controls. Thalamic volumes (total, anterior, and posterior volumes) of patients and controls were compared.

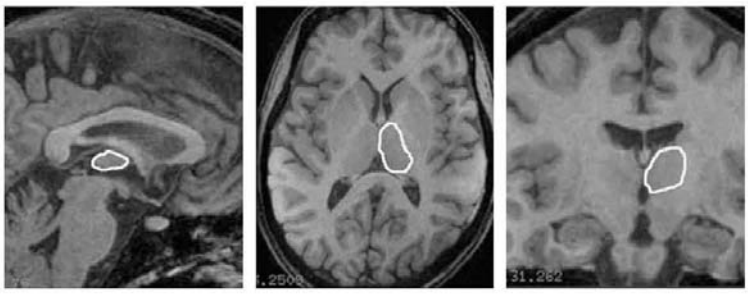

Fig. 1. Example of thalamic segmentation in sagittal, axial, and coronal T1 slices using the Display software (Montreal Neurological Institute).

Student's t test was used to compare the volumes of all patients with IGEs with those of the control group. Analysis of variance (ANOVA) followed by a Tukey post hoc test was used for pairwise comparison of the total, anterior, and posterior thalamic volumes between patients and controls. This procedure includes a post hoc correction for multiple comparisons. ANOVA was also used to analyze possible age differences among groups.

To investigate the relationship between age, age at seizure onset, duration of epilepsy, and thalamic volumes, we used the Pearson correlation test. Duration of epilepsy was defined as the time between the first and last seizures.

3. Results

3.1. Clinical features

Most of the patients in the JME (60%, 43/71) and AE (70%, 19/27) groups were taking valproate as the main AED. In the GTCS group, the percentage of patients taking valproate was lower than in the other groups (16%, 8/49), and the most frequently used AED was carbamazepine (41%, 20/49).

Statistical analysis showed that patients in the AE group were younger than patients in the GTCS group ($P = 0.01$). There was no statistical difference among the other groups in age at MRI evaluation ($P > 0.2$). Duration of epilepsy was 14 ± 11 years (mean $\pm$ SD) in the JME group (range = 0–47), 16 ± 11 years in the AE group (range = 2–40), and 12 ± 11 years in the GTCS group (range = 0–44) ($P > 0.2$).

There was good seizure control in the three groups: 72% (51/71), 67% (18/27), and 88% (43/49) of the patients in the JME, AE, and GTCS groups, respectively, were seizure-free at least 2 years. It had been a mean of 4 ± 3 years (range = 0–14), 2 ± 2 years (range = 0–8), and 5 ± 3 years (range = 1–19) since the last seizure in the JME, AE, and GTCS groups, respectively.

3.2. EEG features

At the time of MRI acquisition, 96 of the 147 (65%) patients (49 with JME, 24 with AE, and 23 with GTCSs) had at least one EEG showing generalized SWDs with normal background.

3.3. Total thalamic volumes

The mean thalamic volume of the controls was $9312 \pm 615\ mm^3$, and that of the patients, $9638 \pm 575\ mm^3$. Comparison between patients and controls showed increased thalamic volume in patients with IGEs ($P = 0.001$).

When compared with controls, patients with JME ($9660 \pm 578\ mm^3$) and AE ($9708 \pm 544\ mm^3$) had an increased total thalamic volume ($P = 0.01$ and 0.03, respectively). Thalamic volumes of patients with GTCSs ($9569 \pm 594\ mm^3$) were not statistically different from those of controls ($P = 0.1$).

3.4. Anterior and posterior volumes

The mean anterior thalamic volume in the control group was $4314 \pm 423\ mm^3$, and the mean posterior thalamic volume was $4999 \pm 426\ mm^3$. Patients with IGEs as a single group had an increased mean anterior thalamic volume ($4530 \pm 365\ mm^3$, $P = 0.001$) compared with controls. Their mean posterior thalamic volume was not different from that of controls ($5114 \pm 443\ mm^3$, $P = 0.127$).

Anterior volumes were increased in the subgroups of patients with JME ($4532 \pm 403\ mm^3$) and AE ($4579 \pm 412\ mm^3$), but not in the GTCS group ($4500 \pm 270\ mm^3$), when compared with those of controls ($P = 0.02$, 0.01, and 0.08, respectively). Posterior thalamic volumes of subgroups of patients were not different from those of the controls: JME $5137 \pm 404\ mm^3$, AE $5137 \pm 463\ mm^3$, and GTCS $5068 \pm 490\ mm^3$ ($P = 0.5$, 0.3, and 0.8, respectively).

3.5. Anterior volumes in patients with JME and absence seizures

To investigate the relationship between increased anterior thalamic volumes and absence seizures, we divided JME patients into two groups: with and without typical absence seizures. In the former, we included patients with well-described, characteristic absences reported by the patient or an observer regardless of the frequency.

Of the 71 patients with JME, 28 (40%) had typical absence seizures. In the group of patients with JME with absence seizures, there were 21 women, for whom mean age was 32 ± 8 (range = 18–48), mean age at seizure onset was 12 ± 6 (range = 2–24), and mean time since the last seizure was 3 ± 2 years (range = 0–10). In this group, 75% (21/28) were taking valproate as the main AED and 68% (19/28) were seizure-free at least 2 years. In the group of patients with JME without absences, there were 25 women, for whom mean age was 31 ± 10 (range = 15–63), mean age at seizure onset was 14 ± 7 (range = 0–43), and mean time since last seizure was 4 ± 3 years (range = 0–14). In this group, 51% (22/43) were taking valproate as the main AED and 75% (32/43) were seizure-free at least 2 years. There were no differences in these clinical data between patients with and without absences.

Compared with those of controls, anterior thalamic volumes of patients with JME and typical absences ($4568 \pm 389\ mm^3$) were statistically significantly increased ($P = 0.03$). The anterior volumes of patients with JME without typical absences ($4508 \pm 416\ mm^3$) were not different from those of controls ($P = 0.07$). The posterior thalamic volumes were not different from those of controls (JME with absences: $5099 \pm 398\ mm^3$, JME without absences: $5161 \pm 411\ mm^3$, $P = 0.7$ and 0.2).

Fig. 3 is a graphic representation of group comparisons of anterior and posterior thalamic volumes.

There was no relationship between age, age at seizure onset, duration of epilepsy, and thalamic volumes in the IGE groups ($P > 0.1$).

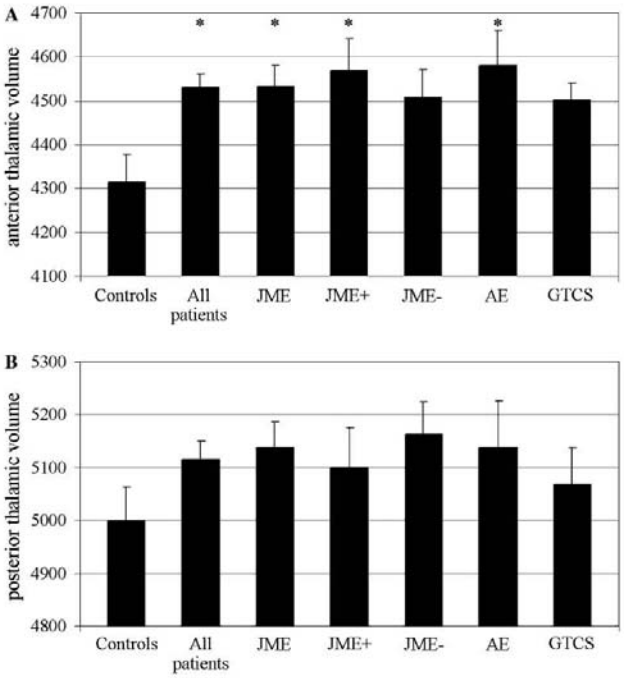

Fig. 3. Graphic representation of the anterior (A) and posterior (B) mean thalamic volumes and SE in all groups (patients and controls). *$P < 0.05$. JME, juvenile myoclonic epilepsy; AE, absence epilepsy; GTCS, generalized tonic clonic seizures; +, positive history for absences, −, negative history for absences.

4. Discussion

This study showed, for the first time, increased thalamic volumes in a large group of patients with IGE. A previous study evaluating the thalamus in 17 patients with IGEs, not specifying the subsyndrome, failed to demonstrate differences when compared with controls [10]. In another study quantifying subcortical volumes, including the thalamus, thalamic volumes of 11 patients with IGEs (5 with JME, 2 with juvenile absence epilepsy, and 4 with GTCSs on awakening) did not differ from those of controls [11]. However, the authors identified smaller subcortical volumes in the IGE patients mainly because of bilateral putaminal reduction [11]. The divergence from these results noted in our study may be explained by three main points: (1) the small number of patients evaluated in the previous studies, (2) differences in the qualities of images and in the protocol for volumetric measurements, and (3) clinical distinction of subsyndromes. Thalamic volumes of 55 patients (28 with JME and 27 with AE) with absence seizures were evaluated in our study. There is no clear clinical description in the previous studies, but the number of patients with absences was smaller. Seeck et al. analyzed only 2 patients with juvenile absence epilepsy [11].

The thalamus is anatomically divided into anterior and posterior nuclei. This division also reflects the function of this structure. The anterior portion is related predominantly to interconnections with all cortical areas. These communications are so extensive that the functions of these structures are not considered separately. Information provided by almost all sensory systems is conducted to the posterior portion of the thalamus. These sensory impulses are retransmitted to the cortex, also passing through the ventral thalamus [15]. Thalamic relay neurons, thalamic reticular neurons, and cortical pyramidal neurons are believed to participate in the absence seizure mechanism. Thalamic reticular neurons are responsible for the mode of thalamocortical activation, and this population of cells is situated mainly at the anterior portion of the thalamus [16,18]. The exact mechanisms involved in the generation of seizures are not completely defined. Our results showing increased thalamic volumes in patients with absence seizures may reflect inherited abnormalities affecting thalamic reticular neurons. These findings are in agreement with experimental models and imaging studies pointing to an anterior thalamic abnormality in patients with absence seizures. Until now, there has been only evidence of a thalamic dysfunction rather than structural abnormalities in the pathophysiology of generalized SWDs and absence seizures [6,7,9–11].

The IGE subsyndromes are clinically differentiated by the main seizure type and age at seizure onset [1]. Clinical differences between IGEs probably indicate different pathogenesis [19]. MRI spectroscopy revealed metabolic

differences between JME and GTCSs [8]. IGEs also appear to be related to cortical abnormalities [5,20,21]. The present study supports multiple mechanisms for IGE subsyndromes depending on the predominant seizure type. Increased thalamic volumes in patients with absences may reflect the predominance of thalamocortical interactions in this seizure type. Myoclonic seizures also are associated with the thalamocortical loop, but the cortex may significantly participate too [22]. In the GTCS group, the patients presented exclusively with GTCSs and there were no reports of other seizure types. The lack of thalamic abnormality in this group of patients probably reflects a different pathophysiology for GTCSs. According to experimental data, the mechanism is related mainly to the cerebral cortex and the brainstem [23].

There was no relationship between age, age at seizure onset, duration of epilepsy, and thalamic volumes. Despite this, we observed that patients with AE had higher thalamic volumes and worse seizure control. On the other hand, patients with GTCSs had thalamic volumes similar to those of normal controls and better seizure control. It is interesting that the most effective AEDs (valproate and ethosuximide) for absence seizures work by causing a voltage-dependent blockade of T-type calcium currents as one mechanism of action [18,24]. This mechanism is believed to inhibit thalamic neuronal firing. This finding raises the possibility of an association between refractory seizures in IGEs and increased thalamic volumes. These differences in seizure control and the larger proportion of generalized SWDs in the EEGs of patients with absence seizures are possibly related to the increased anterior volumes in these patients. These findings may indicate that the thalamocortical circuitry is more active in patients with absence seizures, and the increased volumes may be the expression of discrete edema or even increased blood flow on the structural MRI scans. It is important to note that, in addition to neuronal size and number, axonal and dendritic arborization also appears to contribute to the density of gray matter observed on MRI scans [25]. Therefore, increased axonal/dendritic density could be another possible explanation for the increased anterior thalamic volumes in these patients.

Thalamic volumes may be associated with the age of patients. However, this is unlikely because the registration of the images in the stereotaxic space reduces the differences and anatomical variations between the studied brains. But even if the normalized volumes were larger in patients with absence seizures simply because of age differences, then this finding once more could reflect activity in the thalamocortical circuitry. IGEs and especially typical absence syndromes such as childhood absence epilepsy are usually self limited. The increased volumes in young patients may indicate that this structure probably remains involved in the epilepsy mechanisms. The characteristics of our population, followed in a tertiary center and consisting mainly of young adults, also support this hypothesis.

The long-term use of AED therapy by our patients raises the question of whether our results can be explained by drug exposure. The thalamic abnormalities were found predominantly in the JME and AE groups. Most of these patients were taking valproate. Valproate may be associated with cerebral atrophy and cognitive decline in neuroimaging studies [26]. The clinical course may be acute or insidious, and the prevalence of asymptomatic cerebral atrophy in patients chronically using valproate is unknown [26]. Our patients did not present these clinical characteristics. Our findings do not seem to be associated with drug exposure because increased thalamic volumes are in the opposite direction of the cerebral changes expected in patients using valproate.

It remains unclear what could be the cause of the increased volumes in patients with IGEs. Our findings do not necessarily reflect structural abnormalities. They may represent, as previously mentioned, adaptative findings or even a peculiarity in the population studied. However, this anatomical difference is corroborated by functional and experimental studies [16,27,28]. Precise volumetry of the thalamus is difficult because of the limitations of MRI. We used software that allows a simultaneous view in three distinct orthogonal planes of the exam. This software optimizes the localization of the anatomic boundaries, increasing the quality and precision of the segmentation. Further investigation is needed, especially with more powerful MRI scanners and new quantitative methods, to confirm our findings.

Complete definition of the underlying subtle structural abnormalities in patients with IGEs will be very helpful for genetic evaluation, mainly in selecting more homogeneous populations for studies, and possibly for clinical management. In conclusion, our study supports the participation of the anterior portion of the thalamus in the pathophysiology of IGEs and, especially, absence seizures.

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4- DISCUSSÃO E CONCLUSÕES

4.1- Discussão

As EGI constituem um grupo bastante amplo de patologias. Em suas expressões clínicas mais típicas, as patologias apresentam distintas apresentações, severidade e prognóstico. Entretanto, muitas vezes, os limites entre as subsíndromes são imprecisos. Além disso, características clínicas e neurofisiológicas por vezes se misturam até mesmo com epilepsias parciais. Devido a esta sobreposição entre as patologias alguns autores sugerem que as EGI seriam um *continuum biológico* entre si e com epilepsias parciais [BERKOVIC ET al., 1987; PANAYIOTOPOULOS, 1997]. Em um lado estariam as epilepsias focais lesionais e no oposto encontraríamos as EGI bem caracterizadas como, por exemplo, EAI típica.

A fisiopatologia das EGI e das descargas eletroencefalográficas generalizadas permanecem em investigação. Todas as hipóteses, desde a centrencefálica até a teoria do foco cortical envolvem a interação cortico-talâmica como principal mecanismo fisiopatológico [GLOOR, 1969; MEEREN et al., 2002]. Os estudos por neuroimagem realizados também apontam para uma alteração localizada em ambas estruturas [WOERMANN et al., 1999; MORY et al., 2003].

A avaliação eletroencefalográfica dos pacientes estudados mostrou uma baixa porcentagem de exames iniciais com anormalidades típicas. Além disso, observamos que os exames seriados auxiliam na caracterização do diagnóstico. Portanto, nosso artigo 1, reforça a necessidade da história clínica detalhada na classificação e no diagnóstico das EGI. As focalidades nos EEGs de pacientes com EGI permanecem em discussão. Observamos estas anormalidades com bastante freqüência em nossos pacientes. Uma das hipóteses para o mecanismo das descargas focais seria a presença de anormalidades estruturais sutis. No estudo 2, procuramos por anormalidades estruturais na RM de alta resolução investigando esta possibilidade. Os EEGs realmente estavam relacionados com anormalidades na RM, no entanto estas eram inespecíficas. Confirmamos novamente que diante de um quadro clínico bem detalhado compatível com EGI principalmente quando referendado pelo EEG, não existem anormalidades estruturais importantes nestes pacientes. Entretanto, as anormalidades encontradas podem exercer um papel no fenótipo clínico e eletroencefalográfico das EGI. Devido à extensa interconexão

entre tálamo e córtex, praticamente todas as regiões do córtex podem interferir no circuito tálamo-cortical. Portanto, lesões aparentemente inespecíficas podem estruturalmente modificar estas relações em um paciente geneticamente predisposto e com outras anormalidades microestruturais.

A avaliação clínica de nossos pacientes evidenciou também uma elevada freqüência de pacientes com CTCG. Acredita-se que epilepsias com CTCG apenas correspondem a 13-15% das EGI. Entretanto, apenas as epilepsias com CTCG ao despertar são mais estudadas [PANAYIOTOPOULOS, 2002]. Observamos em nossa avaliação uma porcentagem maior de pacientes com este diagnóstico. A idade dos pacientes e o critério de seleção mais amplo, incluindo todos os pacientes com crises generalizadas, podem ser responsáveis por esta diferença.

Em seguida utilizamos técnicas quantitativas para avaliar as imagens em questão procurando por anormalidades estruturais sutis. As técnicas de neuroimagem quantitativas consistem em aplicar algoritmos sobre as imagens. Após o processamento das imagens podemos através de programas de computador quantificar determinadas estruturas de interesse. O objetivo deste processo é aumentar a sensibilidade para detecção de anormalidades nos pacientes.

A MBV é uma técnica de análise quantitativa que realiza automaticamente a segmentação da substância cinzenta e permite a comparação entre grupos diferentes de imagens com patologias semelhantes. Este tipo de análise tem como beneficio a redução importante do tempo de interação entre o usuário e o computador. Além disso, devido à segmentação automática outra vantagem é a redução do viés do investigador. Este método pode ser utilizado, devido a sua menor interatividade, com o objetivo de procurar por áreas suspeitas para uma melhor quantificação posterior como nós realizamos. Nossos achados utilizando a MBV, detalhados nos artigos 3 e 4, foram compatíveis com anormalidades estruturais sutis em pacientes com EGI. Mais ainda, a diferença entre as diversas subsíndromes e mesmo a diferença com artigos previamente publicados apóiam a existência de mecanismos ou pelo menos anormalidades distintas mesmo entre grupos classificados como semelhantes.

Deste modo, nossos resultados sugerem a presença de uma patogênese diferente para as diversas EGI. Mecanismos diferentes traduzem patologias distintas que demandam tratamentos específicos. Este achado reforça a necessidade de manter a distinção entre as diversas subsíndromes de EGI. Por outro lado, a diferença entre EGI e epilepsias parciais aparenta ser menor do que previamente estabelecido. A evidência de áreas corticais de anormalidades como descrito em nossos artigos 3 e 4 reforça a existência de alterações estruturais mínimas no córtex cerebral de pacientes com EGI.

O tálamo é uma estrutura fundamental, sobretudo nas crises de ausência. Esta estrutura encontra-se estrategicamente localizada na porção mais interior do cérebro. Sua interação com o córtex é tão exuberante que as duas estruturas não são consideradas isoladamente. O tálamo é dividido em duas porções. A posterior é responsável principalmente pelas conexões aferentes sensitivas [SHERMAN e GUILLERY, 2001]. A maior parte da porção anterior é composta pelo núcleo reticular do tálamo envolvido diretamente na fisiopatologia das crises de ausência [SLAGHT et al., 2002]. Nossas investigações ressaltam que esta estrutura provavelmente encontra-se estruturalmente alterada em pacientes com crises de ausência. A avaliação através da MBV indicou uma maior concentração de substância cinzenta na porção anterior do tálamo. A avaliação seguinte através da volumetria confirmou o achado. Este resultado também é amparado por outros estudos que sugerem uma maior densidade neuronal no tálamo de pacientes com EGI [KOEPP et al., 1997]. Por outro lado, a avaliação neuropatológica do tálamo de animais não evidenciou alterações [SABERS et al., 1996]. Os achado por neuroimagem confirmam deste modo, a participação da porção anterior do tálamo na fisiopatologia das crises em pacientes com crises de ausência.

As anormalidades encontradas no circuito tálamo-cortical provavelmente são moduladas por alterações genéticas. Assim, as diferentes características clínicas estariam relacionadas a diferentes anormalidades estruturais ou a nível molecular ocasionadas por genes modificadores [DURNER et al., 2001]. A dificuldade em encontrar um único gene responsável pelas EGI e mesmo pelas subsíndromes provavelmente também está relacionada a estas diferenças [DELGADO-ESCUETA et al., 1999]. Em famílias mais homogêneas, heranças monogênicas bem características foram descritas

[COSSETE et al., 2002]. Para a identificação dos genes responsáveis pela EGI a interação entre a avaliação clínica, eletroencefalográfica e de neuroimagem será fundamental.

A expressão diferente entre epilepsias parciais e generalizadas pode estar relacionada com os diferentes circuitos neuronais envolvidos na epileptogênese das crises. Deste modo, quando o predomínio fisiopatológico é da interação tálamo-cortical como nos pacientes avaliados, o paciente apresentaria uma epilepsia com fenótipo semelhante às EGI. Por outro lado, quando este predomínio encontra-se nas regiões corticais a epilepsia se enquadraria nas epilepsias parciais. Do mesmo modo, dependendo da localização das anormalidades corticais bem como de outras interações, conforme sugere também nosso artigo 3, o tipo predominante de crise pode ser diferente.

A presença de focalidades na semiologia, EEG e RM quantitativa confirma que parte das EGI apresenta uma base focal. Este achado encontra-se em acordo com as descrições de anormalidades estruturais presentes nos raros estudos anatomo-patológicos [MEENCKE e JANZ, 1984]. Investigações apontam também para alterações cognitivas em pacientes com EGI caracterizadas por disfunções no lobo frontal [SWARTZ et al., 1996; SONMEZ et al., 2004]. Desta forma, nossos estudos, sustentados pelas evidências apontadas pela literatura, fortalecem a hipótese de que as EGI não são necessariamente epilepsias legitimamente generalizadas.

A volumetria (artigo 5) confirmou o achado presente na MBV. Observamos um maior volume talâmico nos pacientes com EGI sustentando sua participação na fisiopatologia deste tipo de crise em humanos. O programa utilizado proporciona uma melhor identificação dos limites anatômicos visto que permite a visualização das imagens em três planos distintos. O significado deste aumento de volume é difícil de ser precisado. Novos estudos são necessários. Este achado pode refletir edema ou alterações no fluxo sanguíneo relacionados ao funcionamento do tálamo anterior, sobretudo nas crises de ausência. Ou ainda aumento da árvore dendrítica e número de sinapses, que influenciam o volume de substância cinzenta. Outra hipótese seriam alterações estruturais relacionadas aos próprios neurônios talâmicos ou mesmo a conectividade desta região.

4.2- Conclusões

1- Existem indícios da presença de anormalidades estruturais em pacientes com EGI caracterizadas por focalidades no EEG e anormalidades estruturais inespecíficas na RM.

2- O circuito tálamo-cortical encontra-se envolvido na patogênese das EGI e, sobretudo das crises de ausência.

3- A neuroimagem quantitativa pode fornecer dados valiosos sobre a fisiopatologia das EGI e pode contribuir na identificação de lesões sutis não observadas na análise visual.

4- A presença de focalidades nos pacientes com EGI sugere uma base focal mesmo para as epilepsias generalizadas. É provável que o termo "generalizado", derivado do achado eletroencefalográfico, futuramente não será aplicado a grande parte das EGI.

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6- ANEXOS

Aprovação do projeto de pesquisa pelo Comitê de Ética Médica da Faculdade de Ciências Médicas da Universidade Estadual de Campinas

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(Grupo III)

PARECER PROJETO: N° 478/2004

I-IDENTIFICAÇÃO:

PROJETO: **"EPILEPSIA GENERALIZADA IDIOPÁTICA: CARACTERÍSTICAS CLÍNICAS, ELETROENCEFALOGRÁFICAS E DE NEUROIMAGEM"**
PESQUISADOR RESPONSÁVEL: Luiz Eduardo Gomes Garcia Betting
INSTITUIÇÃO: Hospital das Clínicas/UNICAMP
APRESENTAÇÃO AO CEP: 20/09/2004
APRESENTAR RELATÓRIO EM: 19/10/05

II - OBJETIVOS

Identificar pacientes e familiares com Epilespsia Generalizada Idiopática (EGI) e avaliar as caracteristicas clinicas e eletromagnéticas, com a técnica de volumetria, morfometria baseada em voxel e a análise de textura.

III - SUMÁRIO

Amostra será a partir dos primeiros 20 pacientes até obter poder estatísticos em cada grupo de análise. Serão pacientes com diagnóstico de epilepsia, em seguimento ambulatorial do Hospital das Clínicas da UNICAMP, identificados de acordo com a classificação clínico-eletroencefalográfica proposta pela internacional League Against Epilepsy em 1989, através de interrogatório direto como mesmo e com familiares que testemunharam as crises. Os pacientes identificados com EGI no ambulatório de neurologia., e divididos de acordo com as sub-síndromes e com a presença ou não de história familiar positiva. Familiares com história sugestiva de epilepsia também serão avaliados. Será feita a correlação clínico-EEG nos diversos grupos de EGI. E os exames de EEG serão classificados em típicos e atípicos. Depois será feita a correlação clínico-imageológica, dividindo os pacientes entre as diversas sub-síndromes, avaliando a concentração de substância cinzenta, volumetria do tálamo e textura do tálamo. Serão realizados EEGs seriados em aparelhos de 16 à 32 canais, obtidos de acordo com o sistema 10-20 de colocação de eletrodos, com duração aproximadamente de 20-30 minutos. Serão obtidas imagens RM de alta resolução, após assinatura de TCLE.

IV - COMENTÁRIOS DOS RELATORES

O protocolo está bem estruturado. Não apresenta riscos para o paciente, a não ser o desconforto e ser submetido a exames de ressonância magnética, com duração de 40-90

minutos. E este desconforto está descrito no TCLE. O TCLE está muito longo e com letras miúdas, podendo dificultar a leitura e compreensão do sujeito. Há apoio da FAPESP.

Recomendação: que o TCLE seja mais resumido, com letras maiores para facilitar a leitura e compreensão do sujeito da pesquisa.

V - PARECER DO CEP

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

O conteúdo e as conclusões aqui apresentados são de responsabilidade exclusiva do CEP/FCM/UNICAMP e não representam a opinião da Universidade Estadual de Campinas nem a comprometem.

VI - INFORMAÇÕES COMPLEMENTARES

O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

Pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.1.z), exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade do regime oferecido a um dos grupos de pesquisa (Item V.3.).

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4.). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projeto do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, Item III.2.e)

Relatórios parciais e final devem ser apresentados ao CEP, de acordo com os prazos estabelecidos na Resolução CNS-MS 196/96.

VII - DATA DA REUNIÃO

Homologado na X Reunião Ordinária do CEP/FCM, em 19 de outubro de 2004.

Profa. Dra. Carmen Sílvia Bertuzzo
PRESIDENTE DO COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

Termo de consentimento livre e esclarecido para a participação no estudo

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

Título do projeto: Epilepsia Generalizada Idiopática: Aspectos Clínicos, Eletroencefalográficos e de Neuroimagem.

Investigador principal: Dr. Luiz Eduardo Gomes Garcia Betting

OBJETIVO DA PESQUISA:

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

A ressonância magnética é uma técnica capaz de produzir imagens de alta qualidade e resolução (nitidez) anatômica, assim como informações sobre a bioquímica dos tecidos. A ressonância magnética produz imagens em cortes que são parecidos com as imagens produzidas pela tomografia computadorizada, porém com maior resolução (nitidez) e sem a exposição aos raios X. Essas imagens também irão produzir informações

bioquímicas que serão úteis para melhor definição do diagnóstico e tratamento. O objetivo principal desse estudo é determinar a importância dessas informações bioquímicas e estruturais.

PROCEDIMENTO:

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

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

VANTAGENS:

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

Título do projeto: Epilepsia Generalizada Idiopática: Aspectos Clínicos, Eletroencefalográficos e de Neuroimagem.

Investigador principal: Dr. Luiz Eduardo Gomes Garcia Betting

RISCO E DESCONFORTO:

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

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

REQUERIMENTOS:

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

SIGILO:

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

FORNECIMENTO DE INFORMAÇÃO ADICIONAL:

Eu entendo que posso requisitar informações adicionais relativas ao estudo a qualquer momento. O Dr. Luiz Eduardo Gomes Garcia Betting, tel (019) 3788-7292 estará disponível para responder minhas questões e preocupações. Em caso de recurso, dúvidas ou reclamações contactar a secretaria da Comissão de Ética da Faculdade de Ciências Médicas-UNICAMP, tel. (019) 3788-7232.

RECUSA OU DESCONTINUAÇÃO DA PARTICIPAÇÃO:

Eu entendo que a minha participação é voluntária e que eu posso me recusar a participar ou retirar meu consentimento e interromper a minha participação no estudo a qualquer momento sem comprometer os cuidados médicos que recebo atualmente ou receberei no futuro no HC-UNICAMP. Eu reconheço também que o Dr. Luiz Eduardo Gomes Garcia Betting pode interromper a minha participação nesse estudo a qualquer momento que julgar apropriado.

Universidade Estadual de Campinas
Departamento de Neurologia

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

Título do projeto: Epilepsia Generalizada Idiopática: Aspectos Clínicos, Eletroencefalográficos e de Neuroimagem.

Investigador principal: Dr. Luiz Eduardo Gomes Garcia Betting

Eu confirmo que o(a) Dr(a)._____

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

_____

Nome do participante ou responsável

_____

Assinatura do participante ou responsável data

_____

Nome da testemunha

_____

Assinatura da testemunha data

RESPONSABILIDADE DO PESQUISADOR:

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

_____

Nome do pesquisador ou associado

_____

Assinatura do pesquisador ou associado data