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CONTROLE DE CRISES DE QUEDA (*DROP ATTACKS*) COM CALOSOTOMIA POSTERIOR SELETIVA : RESULTADOS E DADOS ANÁTOMO-RADIOLÓGICOS E PROGNÓSTICOS

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Pontifícia Universidade Católica
do Rio Grande do Sul

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Tese apresentada ao Programa de Pós-graduação em Medicina e Ciências da Saúde da Escola de Medicina da PUCRS, para obtenção do título de Doutor em Medicina.

Orientador: Prof. Dr. André Luis Palmini

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Local da pesquisa

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Ao meu querido pai,
Dr. Leovegildo Frigeri,
que esteve sempre ao meu lado
todos estes anos.

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À minha mãe e meu irmão, fontes de inspiração para mim.

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RESUMO

No programa de cirurgia da epilepsia de Porto alegre (PCE) do HSL PUCRS, os pacientes candidatos à calosotomia posterior seletiva representam cerca de 5% dos casos ditos “cirúrgicos”. Entretanto, estes pacientes geralmente apresentam epilepsias generalizadas graves e de difícil controle medicamentoso com crises de atonia (drop attack) que são particularmente importantes, pois levam a quedas inesperadas com consequentes traumas repetidos e risco de lesões graves e morte por trauma de crânio grave. Este quadro catastrófico não permite que o paciente e seus familiares levem uma vida perto do normal. A ameaça de uma crise de queda iminente faz com que todos envolvidos no dia a dia do paciente estejam em permanente estado de alerta.

O corpo caloso é o maior feixe de fibras comissurais do encéfalo e a calosotomia, em suas diferentes variações e extensões, tem por objetivo retardar a propagação e sincronização das descargas epileptogênicas entre os hemisférios cerebrais e, assim, diminuir ou cessar as crises de drop attacks. A calosotomia é um tratamento desconectivo paliativo, indicado para pacientes com crises epilépticas generalizadas que apresentam crises de drop attack e que não sejam candidatos à cirurgia ressectiva, bissincronia secundária no eletroencéfalograma (EEG), independente da etiologia da epilepsia.

Os objetivos deste trabalho são apresentar os resultados cirúrgicos (controle de drop attacks) dos pacientes submetidos à calosotomia posterior seletiva e definir fatores que influenciem neste resultado, refinando a indicação cirúrgica. Outro objetivo é definir a extensão necessária de ressecção do corpo caloso para um bom controle das crises de drop attacks.

Analisamos os resultados cirúrgicos e características demográficas em 51 pacientes. Destes, 27 pacientes realizaram ressonância nuclear magnética e 18 tractogtrafia pós operatória para correlacionar a extensão e a natureza das fibras ressecadas com os resultados cirúrgicos. Correlacionamos também as características demográficas (idade e tempo de epilepsia na cirurgia, idade de início das crises e etiologia) com os resultados cirúrgicos de controle de crises dequeda.

Os principais resultados foram que a calosotomia posterior seletiva mostrou-se um tratamento efetivo no controle dos drop attacks uma vez que a diminuição global da frequência de crises de queda foi de 89,3% (p<0,001). Pacientes com menor idade no momento da cirurgia e com menor duração de epilepsia tiveram significativamente maior propabilidade de atingirem um resultado mais favorável (p<0,001). A extensão da ressecção do corpo caloso não se correlacionou com resultado cirúrgico (r-0.02) desde que fossem ressecadas as fibras que conectam as áreas motoras primária e motora suplementar caudal. Por fim, na tractografia pós operatória, a presença de fibras residuais conectando a áreas motora suplementar rostral e pré motora não parece ter correlação com o controle dos drop attacks.

Palavras-chave: epilepsia, corpo caloso, calosotomia posterior seletiva, drop attacks.

ABSTRACT

In the Porto Alegre Epilepsy Surgery Program (PCE) of the HSL PUCRS, patients candidates for posterior selective calosotomy represent about 5% of the so-called "surgical" cases. However, these patients usually present severe refractory generalized epilepsies with drop attacks, which are particularly important because they lead to unexpected falls and risk of serious injury and death from severe cranial trauma. This catastrophic picture does not allow the patient and his / her relatives to live a normal life. The threat of an imminent unexpected fall keeps all involved in the patient's daily care permanently alert.

The corpus callosum is the largest commissural fiber bundle in the brain and callosotomy, in its different variations and extensions, has the objective of prevent propagation and synchronization of epileptogenic discharges between the cerebral hemispheres and, therefore, to reduce or stop drop attacks. Callosotomy is a palliative treatment, indicated for patients with generalized epileptic seizures with drop attacks, who are not candidates for resective surgery and have secondary bissynchronic discharges in the electroencephalogram (EEG), regardless of the etiology of epilepsy.

The objectives of this study are to present the surgical results (drop attacks control) of patients who had selective posterior calosotomy and to define correlation factors with the result, thus refining the surgical indication. Another objective is to define the necessary extension of corpus callosum resection for a satisfactory control of drop attacks.

Surgical outcomes and demographic characteristics in 51 patients were analyzed. Twenty seven patients had post-operative magnetic nuclear resonance (MRI) and 18 tractogtraphy to correlate the extent and nature of the resected fibers with surgical results. We also correlated the demographic characteristics (age and duration of epilepsy in surgery, age at seizure onset and etiology) with surgical results.

Selective posterior callosotomy was effective in controlling atonic falls with an overall 89, 3% decrease in drop attacks frequency ($p < 0.001$). Younger patients and with shorter duration of epilepsy at surgery are significantly more likely to achieve a more favorable outcome ($p < 0.001$). The extent of resection of the posterior corpus callosum was not correlated with surgical outcome (r-0.02), however, the fibers connecting the primary and supplementary caudal motor areas were resected in all patients. Finally, in postoperative tractography, the presence of residual fibers interconnecting homologous pre-motor and rostral supplementary motor areas does not seem to correlate with control of atonic falls.

Key words: epilepsy, corpus callosum, posterior selective callosotomy, drop attacks.

LISTA DE ABREVIATURAS

CC	Corpo Caloso
DTI	Imagem por Tensor de Difusão.
EEG	Eletroencéfalograma
M1	Área Motora Primária
PUCRS	Pontificia Universidade Católica do Rio Grande do Sul
RNM	Ressonância Nuclear Magnética
SMA	Área Motora Suplementar
VNS	Estimulação do Nervo Vago

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1.1 APRESENTAÇÃO

O interesse pela cirurgia de epilepsia surgiu durante a graduação na faculdade de medicina da Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), onde fiquei muito impressionado com os resultados obtidos nos pacientes submetidos a este tipo de tratamento. A mudança de vida obtida por estes pacientes e a alegria dos mesmos e de suas famílias durante as consultas de seguimento era algo que me causava grande entusiasmo. Ao ser aprovado e iniciar o programa de residência médica no Hospital São Lucas da PUCRS, eu tive a oportunidade de ter um contato próximo com a rotina de um serviço de referência em epilepsia, seus resultados e desafios.

Ao mesmo tempo em que cirurgia de epilepsia proporciona uma melhora significativa no controle das crises e na qualidade de vida dos pacientes, ela é também tecnicamente desafiadora para o neurocirurgião. A convivência diária com os doutores Eliseu Paglioli Neto, Eduardo Paglioli, André Palmini e Ney Azambuja despertaram em mim a vontade de poder contribuir no serviço como neurocirurgião e um grande interesse pelo tema. Ao acompanhar rotineiramente as cirurgias, me dei conta do desafio que tinha pela frente no que se refere aos desafios técnicos de um procedimento deste porte.

Em 2007 quando participava de um congresso no Japão, conheci pessoalmente o Dr. Albert Rhoton Jr., maior autoridade mundial em micro neuroanatomia cirúrgica e vislumbrei a chance de aprender a fundo as nuances anatômicas do cérebro em seu laboratório na Universidade da Florida, nos Estados Unidos da America. Fui aceito como seu fellow e passei um período de quase dois anos em seu laboratório de anatomia dissecando, estudando e publicando artigos sobre o tema. O período em Gainesville foi de grande amadurecimento e construção de uma base sólida em neuroanatomia, algo fundamental para a realização das cirurgias.

Ao retornar para Porto Alegre em 2014, iniciei como neurocirurgião do programa de cirurgia de epilepsia da PUCRS. Na época estava em fase final um estudo sobre os resultados clínicos dos pacientes submetidos à calosotomia posterior seletiva como tratamento para crises do tipo drop attacks. Estudo este publicado na revista Neurology em outubro de 2016. Os resultados extremamente positivos da técnica criada pelo Dr. Eliseu Paglioli Neto, surpreenderam a comunidade científica da área. Do estudo citado surgiu a ideia e a vontade de aprofundar o assunto e encontrar algumas respostas para questões ainda não bem esclarecidas em relação a este procedimento. A curiosidade de saber porque uma minoria de pacientes não apresentavam um resultado tão exuberante.

Esta tese representa um aprofundamento do estudo das variáveis ligadas ao resultado clínico e discute alguns fatores relacionados a estes pacientes e que devem servir de base para futuras indicações e planejamentos cirúrgicos. O artigo publicado em 2016 e contido na sessão de anexos (Selective posterior callosotomy for drop attacks: A new approach sparing pre frontal conectivity) constitui a base desta dissertação e reflete o processo de construção e amadurecimento científico do tema. Neste estudo procurei integrar e analisar estatisticamente diferentes fatores ligados ao prognóstico destes pacientes.

Esta tese está organizada em um manuscrito em formato de publicação que está em fase final de análise em periódico de circulação internacional, além de dois artigos em anexo já publicados. O corpo da tese constitui-se de uma introdução com descrição da técnica operatória e revisão da literatura seguidos pela descrição dos objetivos principais e secundários. A seguir é reproduzido o manuscrito, em inglês, no formato em que foi enviado para publicação. O manuscrito inclui detalhada descrição da metodologia empregada, análise dos resultados e discussão que contextualiza os achados com o estágio atualda literatura médica. Nos anexos estão reproduzidas as tabelas e ilustrações referentes ao trabalho. As referências bibliográficas encontram-se no final da revisão da literatura. As referências do manuscrito submetido para publicação, encontram-se no final do mesmo.

1.2 ASPECTOS GERAIS

A epilepsia é uma doença bastante prevalente com manifestações bem características que a tornam bastante conhecida do público leigo. No passado a doença era cercada de superstições e o seu portador era estigmatizado no seu grupo social sendo muitas vezes considerado uma “aberração da natureza” ou mesmo até ”possuído”. Ainda hoje, o paciente com epilepsia sofre preconceito e exclusão social.

Cerca de 70-80% dos pacientes com epilepsia obtém bom controle das crises com a terapia medicamentosa. Entretanto, aproximadamente 30% não têm um controle satisfatório e cerca de metade pode se beneficiar do tratamento cirúrgico. Mesmo quando não é possível a realização de uma cirurgia curativa, procedimentos paliativos podem melhorar significativamente a qualidade de vida dos pacientes e por consequência de suas famílias e/ou cuidadores.

Infelizmente, mesmo sendo um tratamento promissor, muitos pacientes não têm acesso a um centro de refêrencia para o manejo adequado e o tempo entre diagnóstico da doença e seu tratamento definitivo pode ser de dezenas de anos. Não raramente, procedimentos cirúrgicos bem sucedidos chegam tarde na vida dos pacientes para reverter as consequencias cognitivas, sociais e psicologicas das repetidas crises que ocorrem justamente durante o período crítico de aquisição de habilidades interpessoais e educacionais. Estes são pacientes livres de convulsões mas que ficam prejudicados para o resto de suas vidas.

As crises do tipo drop attack, são particularmente debilitantes e incluem eventos atônicos, contrações tônicas, mioclonias maciças e não raramente uma combinação destes levando à quedas súbitas ao solo. Este tipo de crise tem um impacto negativo na qualidade de vida dos pacientes e no curso da doença. O perfil cognitivo e comportamental destes pacientes declina severamente com o passar dos anos e o risco de acidentes com lesões traumáticas nestes pacientes é alto e não raramente necessitam o uso constante de equipamentos de proteção, como capacetes por exemplo. A calosotomia é uma boa opção terapêutica para este tipo de crise, pois a redução da frequência das quedas está bem documentado na literatura (1-18).

1.3 O CORPO CALOSO

A substância branca do cérebro contém três tipos de fibras: fibras de associação, interconectando diferentes áreas corticais do mesmo hemisfério cerebral; fibras comissurais, conectando os dois hemisférios cerebrais e fibras de projeção conectando a cortex cerebral com partes mais caudais do cérebro e também com a medula espinhal.

A antomia do corpo caloso tem recebido muita atenção nos últimos anos devido ao número crescente de calosotomias feitas para a remoção de tumores intraventriculares, bem como para o tratamento de epilepsias generalizadas de difícil controle. Ele constitui o maior feixe de fibras comissurais do cérebro humano, sendo responsável por aproximadamente 70-80% da conexão entre os hemisférios cerebrais com mais de 200 milhões de projeções axonais transversais (19-21). Sua forma final é atingida na vigésima semana após a concepção, porém mudanças estruturais continuam ocorrendo até a adolescência (22). Constituído por axônios mielinizados que cruzam a linha média no cérebro em evolução para conectar regiões homólogas dos hemisférios cerebrais, está localizado na porção basal da fissura inter-hemisférica e constitui o teto dos ventrículos laterais (23, 24). É dividido em quatro partes de anterior para posterior: rostro, joelho, corpo e esplênio e é circundado pelo giro do cíngulo. Na linha média, sua metade anterior está localizada profundamente ao giro frontal superior e sua porção mais posterior ao lóbulo paracentral que corresponde a área motora e sensitiva na face medial do cérebro (25, 26). Dentro de cada hemisfério cerebral, suas fibras se abrem como um leque para todos os lobos formando a radiação calosa. As fibras que se dirigem anteriormente, para os lobos frontais, se chamam forceps minor, enquanto as fibras que se dirigem posteriormente, em direção aos polos occipitais, se chamam forceps major (25). O suprimento arterial do corpo caloso é provido pelo sistema carotídeo com a artéria pericalosa (ramo da artéria cerebral anterior), exceto o esplênio que é irrigado pelos ramos terminais e coroideos da artéria cerebral posterior (sistema vertebro-basilar) (25). O corpo caloso é responsável pela conexão entre os hemisférios cerebrais, facilitando a comunicação através de mecanismos fisiológicos excitatórios e inibitórios nas mais diversas funções envolvendo linguagem, cognição, memória, funções integrativas e até coordenação de movimentos.

Desta maneira, o corpo caloso é a principal via de propagação contralateral de crise epiléticas em áreas interconectadas, sendo o responsável pelo bissincronismo secundário, que é a rápida propagação de descargas de um hemisfério para o outro. Em 1940, um estudo realizado em macacos demonstrou que a propagação deuma descarga epiléticade um hemisfério para o outro, ocorria total ou quase que totalmente através do corpo caloso (27).

O corpo caloso não é uma estrutura homogênea, no sentido de que as fibras que conectam áreas corticais específicas, transitam por regiões calosas distintas. Em outras palavras, há uma topogtrafia na qual as regiões corticais anteriores estào conectadas através da porção mais anterior do corpo caloso (rostro, joelho e corpo anterior), enquanto as áreas centrais e posteriores estão conectadas pelas porções mais posteriores (istmo e esplênio) (28).

Diversos estudos buscaram descrever a topografia das fibras calosas no corte sagital na linha média (20, 21, 28-31). Porém, como não há nehuma referência anatômico que claramente divida e delimite regiões distintas no corpo caloso, diversos esquemas geométricos foram descritos para subdividir o corpo caloso. Um dos exemplos mais proeminentes é o esquema apresentado por Witelson em 1989 que divide as fibras em cinco sessões verticais baseadas em estudos realizados em primatas (prefrontal, premotor, motor, sensitivo e parietotemporo-occipital) (30). Entretanto, o desenvolvimento da ressonância nuclear magnética por tensor de difusão (DTI) abriu novas possibilidades no entendimento da substância branca do cérebro. A imagem por tensor de difusão (DTI) é uma sequência de ressonância nuclear magnética (RNM) que fornece informações sobre a microestrutura da substância branca cerebral através de vários índices como a anisotropia fracionada e a difusividade média. Este método permite determinar a organização tecidual das fibras da substância branca através da análise da difusividade da água no tecido cerebral de forma quantitativa permitindo a imagem dos tratos de substância branca ou tractografia (32). Estudos mais recentes baseados nesta ferramenta têm demonstrado diferenças consideráveis em relação ao esquema clássico de divisão de origem das fibras no corpo caloso humano particularmente no que se refere aos feixes de fibras originados no cortex motor e pré motor. Ao invés do esquema clássico as fibras motoras cruzam mais posteriormente do que se pensava previamente (20, 29, 31, 33). Somado a isto, estudos de densidade e diametro das fibras comissurais do corpo caloso mostram e fibras com maior diametro, e portanto de condução mais rápida, nas áreas que ligam os cortex motores e sensitivos primários, facilitando assim a propagação de descargas epilépticas para o hemisfério contra lateral (21). Fibras com maior diâmetro são especialmente adequadas na conexão das áreas motoras homólogas pois maior velocidade de condução é necessária para a realização de movimentos coordenados com ambas metades do corpo e ambos os mebros concomitantemente. Assim é plausível uma teoria que a secção de suas fibras seja eficaz no combate a rápida generalização das crises epiléticas, especialmente porque a bissincronia epiléptica das regiões motoras está na origem das crises de queda (1, 2).

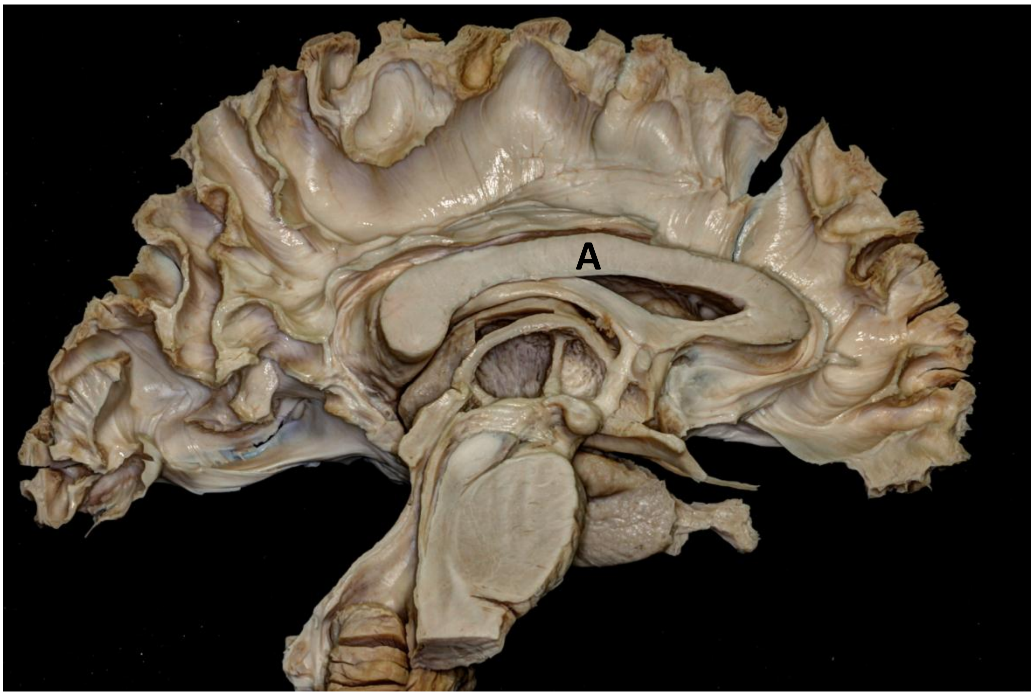


Fig 1. Dissecção anatômica de fibras brancas cerebrais. O corpo caloso (A) é o maior feixe de fibras comissurais do cérebro humano, sendo responsável pela rápida generalização de descargas epilépticas de um hemisfério para outro.

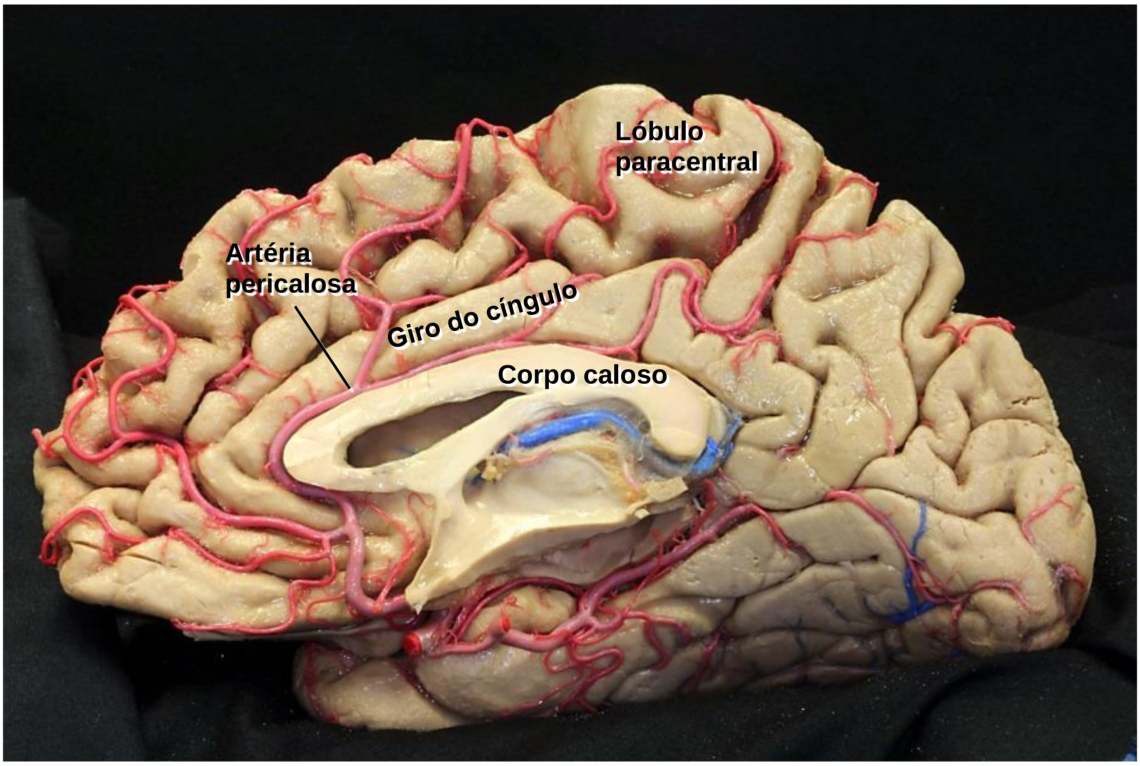


Fig 2. Dissecção anatômica do encefálo. Irrigação arterial do corpo caloso e sua relação com o lóbulo paracentral (área sensitivo-motora) na face medial do cérebro.

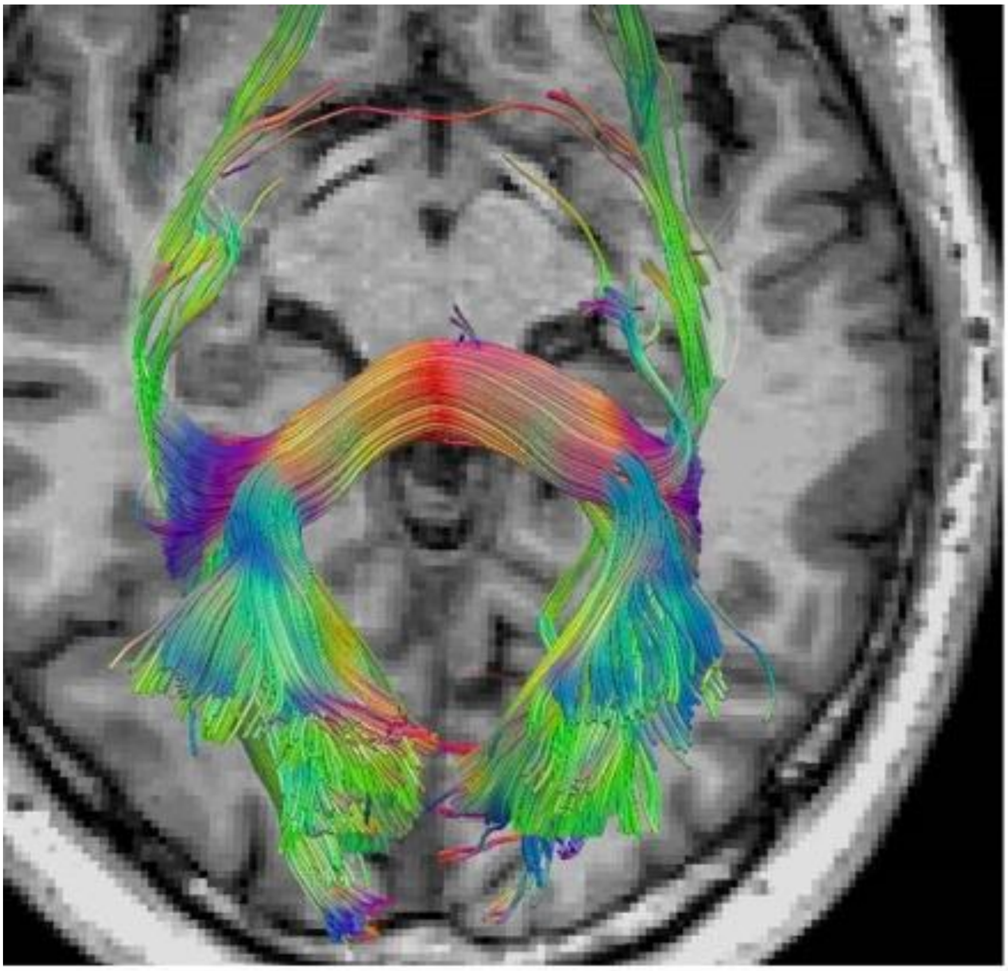


Fig 3. RNM com DTI do copo caloso (Fórceps Major). Fibras do corpo caloso cruzando a linha média na altura do esplênio (feixe de fibras conhecido como forceps major).

1.4 HISTÓRIA

A primeira secção cirúrgica do corpo caloso foi descrita por Dandy em 1922 com o intuito de acessar o terceiro ventrículo (24). Já em 1931 ele seccionou o corpo caloso para abordar um cisto congênito do cavo de um septo pelúcido e cavo vergae em um menino de 4 anos de idade também portador de epilepsia e como consequência inesperada, o paciente ficou livre de crises após o procedimento. Em 1940, os primeiros relatos do mecanismo de propagação de crises para o hemisfério contra lateral através do corpo caloso foram descritos (27) e no mesmo ano Van Wagenen e Herren realizaram a secção do corpo caloso em humanos com o objetivo de controlar crises epiléticas generalizadas (1). Em um de seus estudos mais importantes, eles reportaram uma observação importante em uma série de gliomas de corpo caloso (1, 34):

> **"In the early part of the life history of the tumors in this series, convulsions were common. In late stages, convulsions were much rarer; if they did occur they were unilateral and usually were not accompanied by loss of consciousness. In other words, as the corpus callosum was destroyed generalized convulsive seizures became less frequent."**

Eles também descreveram outras observações importantes. Por exemplo, em um paciente com múltiplos meningeomas, incluindo um meningeoma parafalcino progressivamente se projetando para dentro da substância do corpo caloso, foram documentadas muitas crises epiléticas no início do curso da doença, porém raras crises nos estágios mais avançados. Em outro caso, reportaram um paciente com longa história de epilepsia que demonstrou diminuição da frequência de crises após sofrer hemorragia da artéria cerebral anterior. Baseados nestes casos, eles concluíram que as convulsões ficaram menos frequentes quando as fibras de associação haviam sido destruídas. Destas observações clínicas partiu a ideia de realizar a divisão do corpo caloso com o objetivo de limitar a propagação de descargas epiléticas de um hemisfério a outro do cérebro (1, 34).

Apesar disto, essa modalidade terapêutica não foi aceita pela comunidade científica até muito tempo depois, e após a descrição da primeira série de calosotomias, vinte anos se passaram até uma nova série ser publicada. No início da década de 1960, Bogen reintroduziu a secção do corpo caloso reportando um paciente que ficou completamente livre de crises generalizadas após a realização da cirurgia (35). No entanto, apesar dos bons resultados, o procedimento não ganhou popularidade. A explicação é de que as primeiras comissurotomias envolviam também a secção das comissuras anterior, posterior e massa intermédia do tálamo, o que acrescentava alta morbidade ao tratamento. Apenas em 1975, Wilson introduziu técnicas microcirúrgicas para realizar calosotomias com o objetivo de tratar epilepsias catastróficas e mostrou que a calosotomia era uma boa alternativa à hemisferectomia, em casos selecionados (32). Em 1982, a conferência de Dartmouth, organizada por Wilson e Reeves, reportou o uso da calosotomia para epilepsia generalizada refratária em seis diferentes centros. Desde então, é amplamente aceito de que a calosotomia pode trazer excelentes resultados cirúrgicos em crises generalizadas prevenindo a rápida propagação de descargas de um hemisfério para outro. A síndrome de desconecção pré frontal tem sido descrita após calosotomias anteriores e totais (7). Ela se caracteriza por diminuição na fala espontânea, confusão mental, apatia e mínima interação com o meio. Em 2016, Paglioli publicou a primeira série de pacientes submetidos à calosotomia posterior seletiva, com objetivo de desconectar as áreas motoras e preservar as conexões pré-frontais importantes na cognição, com baixa morbidade cirúrgica e ótimos resultados no controle das crises de atonia e qualidade de vida geral dos pacientes (13).

1.5 PROCEDIMENTO CIRÚRGICO

Uma técnica microcirúrgica adequada é fundamental para evitar a grande maioria das complicações não relacionadas com a secção das fibras do corpo caloso. O estudo minucioso das veias corticais é fundamental na compreensão da anatomia venosa do paciente evitando assim lesões venosas que podem progredir para infarto clinicamente significativo. A reconstrução do exame de ressonância nuclear magnética em T2 é fundamental e a angio RNM com fase venosa pode ser útil em casos em que ainda haja alguma dúvida. Desta maneira é possível variar a posição do flap em alguns centímetros se necessário, otimizando assim a exposição do campo cirúrgico e de uma zona de entrada segura entre ou abaixo das veias de drenagem cortical.

1.5.1 Avaliação e preparo pré operatório

Video EEG e ressonância nuclear magnética são rotineiramente realizados para descartar qualquer anormalidade epilética focal que possa tornar o paciente candidato a uma ressecção curativa. Deficiência intelectual não é contra indicação para a realização do procedimento e apesar de alguns estudos mostrarem resultado pior neste subgrupo de pacientes (4, 36), as crises de atonia podem reduzir significativamente.

O paciente considerado para calosotomia está usualmete em uso de diversas medicações anti epiléticas. A retirada do Ácido Valpróico pelo menos um mês antes da cirurgia é necessário devido à evidência do seu efeito anti plaquetário (37). Ele pode ou não ser substituído por outra medicação de acordo com a necessidade do paciente. Exames pré operatórios de sangue e coagulação são realizados. A anestesia é geral e realizada após obtenção de acesso venoso central. Ultrassom cardíaco para detecção precoce de possível embolia aérea e sonda vesical de demora são colocados. Devido ao posicionamento cirúrgico (semi sentado), a PCO2 deve ser mantida entre 28-33 mmHg para adequado relaxamento cerebral.

1.5.2 Posicionamento cirúrgico

Duas posições podem ser usadas. Uma em deúbito ventral com a face do paciente volatada para o chão, o que diminui o risco de embolia aérea. Entratanto, a maioria dos pacientes são operados em posição semi sentada com a cabeça levemente fletida. Cuidado deve ser tomado na flexão da cabeça para não causar dobramento do tubo endotraqueal. Esta posição favorece o cirurgião por manter a anatomia convencional do paciente e também o campo operátorio mais limpo devido ao não acúmulo de sangue por ação da gravidade. Além disso, facilita também a retração do polo occipital direito da foice do cérebro. Fixador de crânio externo é usado para manter a cabeça em posição durante todo o procedimento.

Fig 4. Posicionamento cirúrgico usado em nosso serviço (semi sentado) para calosotomia posterior seletiva.

1.5.3 Incisão no escalpo, craniotomia e abertura dural

O cabelo do paciente é raspado e as referências anatômicas como a linha média, o astérion, o seio transverso, a sutura lambdóide e a protuberância occipital são identificadas. A incisão é feita em formato de “U” com a abertura voltada para baixo, inicando paramediana à esquerda na altura da protuberância occipital. Sobe por cerca de 4cm quando se curva para a direita, atravessando a linha média até cerca de 3cm da mesma. A seguir curva-se para baixo terminando na altura do início da mesma.

Muitos pacientes selecionados para calosotomia devido à sucessão de traumatismos, têm um osso grosso associado a uma dura matter fina, frágil e aderente, o que faz com se tome cuidado para não lesar a dura e subsequentemente as veias de drenagem cortical. A Craniotomia é feita com cinco trepanações, sendo três na na margem esquerda que fica na linha média sobre o seio sagital superior e outras duas nos cantos laterais da incisão, formando assim uma espécia de retângulo com o lado maior na direção crânio caudal. A craniotomia fica no lado direito, não dominante. Identifica-se então o seio sagital superior, que servirá de referência anatômica como o limite medial da abertura dural. A abertura dural é crucial na calosotomia e deve ser iniciada cerca de 3cm da linha média, em formato de “C”, com a abertura virada para o seio sagital superior. Não deve ser iniciada na linha média ou próxima a ela pelo risco de lesão das veias corticais e dos lagos venosos parasagitais. Devido aos múltiplos traumatismos geralmnete sofridos ao longo da vida por estes pacientes, podem haver aderências entre a dura e as leptomeninges e por este motivo, a visualização do cortex occipital durante a abertura é recomendada enquanto progressivamente se rebate o flap dural em direção à linha média. Na região occipital abaixo da sutura lambdóide geralmente não encontramos veias em ponte no campo operatório, mas se houver necessidade, uma veia pode ser coagulada e seccionada sem maiores consequências (26). O flap dural é então fixado com suturas na linha média, expondo assim o polo e a porção mais superior do lobo occipital até sua transição com o lobo parietal.

1.5.4 Dissecção inter-hemisférica e calosotomia posterior seletiva

Na calosotomia posterior seletiva, a foice do cérebro funciona como afastador do lado esquerdo do campo operatório uma vez que cobre todo o lobo occipital contra-lateral e se estende até o esplênio do corpo caloso. O lobo occipital direito é gentilmente afastado com uma espátula cerebral fixada superiormente à região calcarina. A separaçào das aderências é usualmente feita sem maiores complicações e leva o cirurgião até a região do esplênio, onde se começará a comissurotomia. A cisterna do corpo caloso é aberta observando a posíção da drenagem da veia de Galeno que deve ser preservada. O objetivo desta etapa é conseguir uma boa visuzlização do esplênio do corpo caloso. Após a dissecção e abertura da cisterna, cotonóides cirúrgicos podem ser colocados nas porções superiores e inferiores do campo operatório com a finalidade de auxiliar no afastamento do hemisfério direito. A visualização do corpo caloso com aspecto branco perolado é a referência anatômica mais confiável neste momento.

Inicialmente, a calosotomia posterior é feita aspirando o esplênio, sempre procurando manter-se na linha média. A porção mais basal e posterior do esplênio pode representar um desafio técnico devido a sua íntima relação com a veia de Galeno e as veias cerebrais internas. O esplênio é dividido até a visualização do velum interpositum e nesta região, as artérias pericalosas são pequenas, não representando um obstáculo significativo. A separação do caloso segue por dentro do corpo em direção anterior. Sempre é recomendado manter-se abaixo dos giros do cíngulo, evitando lesões. Após o istmo do corpo caloso, no sentido póstero-anterior, o corpo caloso muda de inclinação, tornando-se mais horizontal. A divisão do caloso segue até o ponto planejado no pré operatório, contemplando metade ou, se tecnicamente possível, os 2/3 posteriores. A aspiração do caloso deve preferencialmente respeitar o epêndima que reveste a cavidade ventricular, sendo não recomendado abrir o ventrículo.

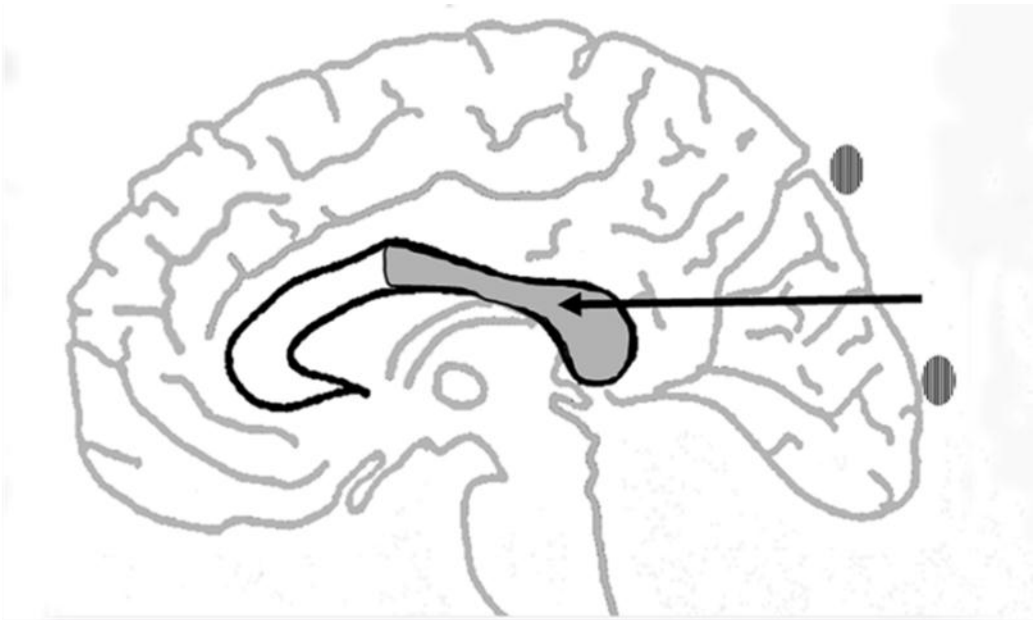


Fig 5. Esquema gráfico demonstrando a proposta cirúrgica da calosotomia posterior seletiva. Aproximadamente 50% posterior do corpo caloso deve ser ressecado para um bom resultado cirúrgico.

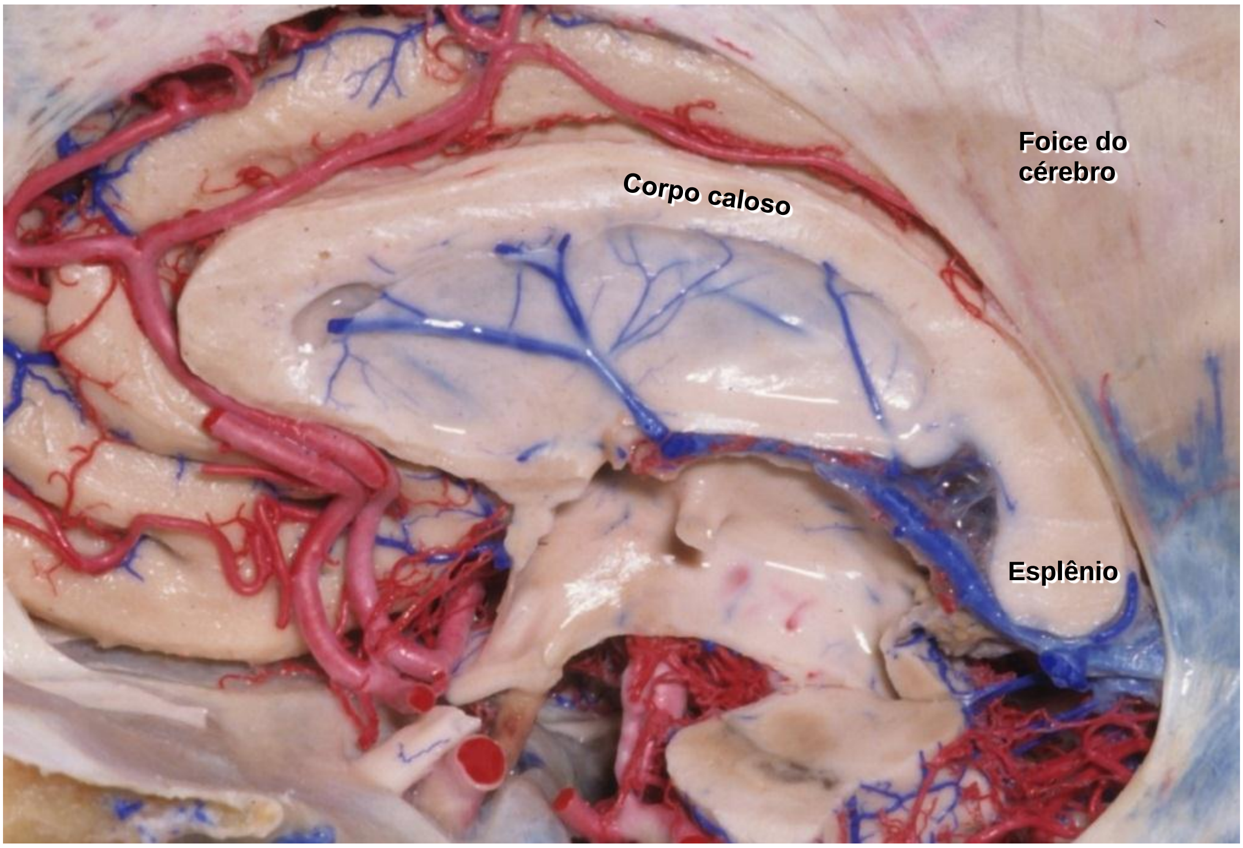


Fig 6.Dissecção anatômica do cérebro demonstrando a foice cobrindo o lobo occipital da altura do esplênio até aproximadamente a metade posterior do corpo caloso.

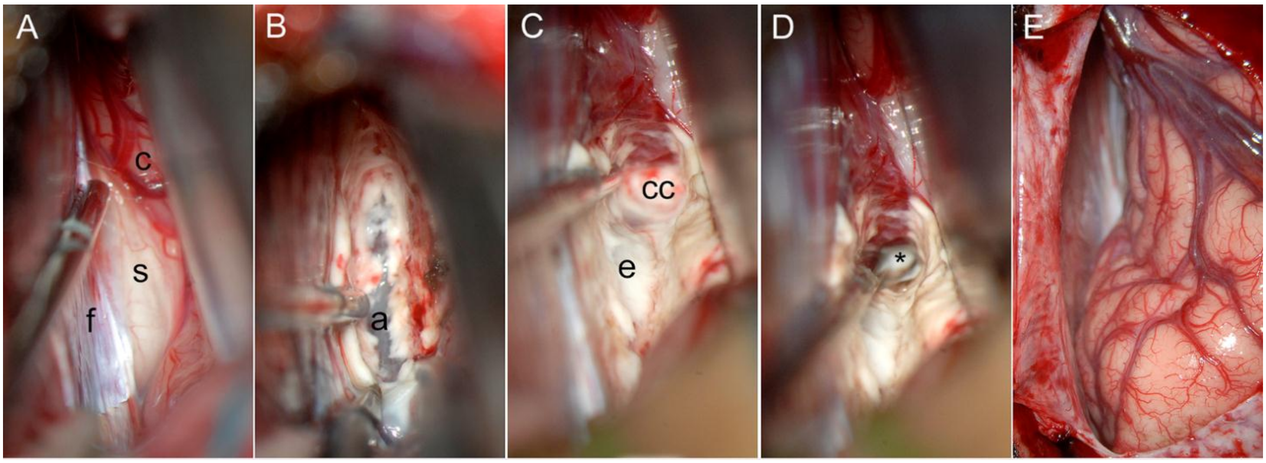


Fig 7. Sequência de fotos transoperatórias demonstrando a calosotomia posterior seletiva. Foice do cérebro (f), esplênio (s), corpo caloso (cc), epêndima (e), átrio ventricular (a).

1.6 CALOSOTOMIA (REVISÃO DA LITERATURA)

Crises epiléticas generalizadas de queda ao solo (drop attack) refratárias ao tratamento medicamentoso envolvem morbidade significativa pelos traumas repetidos, altas doses de drogas anti epiléticas (DAE's) usadas para tratar pacientes que sofrem desta condição e os efeitos deletérios das crises na inteligência e nodesenvolvimento cerebral (38). A calosotomia é um tratamento desconectivo paliativo, geralmente indicado para pacientes com crises epilépticas generalizadas refratárias que apresentam crises de atonia (drop attack), com bissincronia secundária no eletroencéfalograma (EEG), independentemente da etiologia da doença. A calosotomia pode ser realizada em crianças e adultos, e os resultados, apesar de algumas diferenças, são bons em ambos os grupos. Ainda não há uma indicação universalmente aceita para o procedimento e a seleção dos pacientes depende dos critérios do cirurgião ou do centro de epilepsia onde paciente está sendo tratado (18). O fato de que os pacientes com epilepsia catastrófica e descargas sincronizadas bilaterais melhorem com a realização do procedimento não é nenhuma surpresa. A interrupção de aproximadamente 150 milhões de axônios comissurais vai invariavelmente levar à diminuição da transmissão de atividade epilética já que este é o papel inquestionável da calosotomia há décadas (39).

Os pacientes candidatos ao procedimento normalmente têm mais de um tipo de crise epilética e é esperado que permaneçam com crises após a cirurgia. Algumas séries, porém, descrevem subgrupos de pacientes que ficaram livre de diferentes tipos de crise após o procedimento (14). Estudos prévios com follow up longo, mostraram os melhores resultados nos controles das crises de atonia e em algum grau também nas crises tônico-clônico generalizadas. Em alguns pacientes, novos tipos de crises parciais podem surgir após a realização da calosotomia (5, 9, 40). Um estudo de caso descreve um paciente de 9 anos de idade com episódios recorrentes de status epilepticus que não apresentou novos episódios depois que foi submetido à calosotomia total. Neste relato os autores sugerem que o procedimento seja considerado após a falha terapêutica de três linhas de tratamento e terapia de coma farmacológico por duas semanas (41).

A idade do paciente, a duração da epilepsia no momento da cirurgia, além da idade de início das crises parecem ser fatores prognósticos, sendo pacientes jovens e com menos tempo de epilepsia os que possuem maiores chances de ficarem livres de drop attacks, conforme relatam algumas séries de casos (4-6, 11, 14-17, 36, 42). Uma metanálise de 2016 afirma que uma intervenção precoce reduz o progresso da encefalopatia epiléptica e está associada com uma melhor função cognitiva e que a melhora qualidade de vida está associada com a redução de drop attacks mesmo que esta fosse modesta (16). Este estudo demonstrou ainda que os pacientes adultos obtiveram um resultado menos satisfatório do que os pacientes pediátricos. De fato, estudos têm demonstrado que uma epilepsia de longa duração pode predispor à ocorrência de alterações estruturais e microbiológicas em áreas previamente sadias e que isto estaria ligado à persistência de crises epiléticas (31). A cirurgia realizada precocemente após a epilepsia se tornar refratária prediz melhores resultados (16). Em outros tipos de epilepsia focal, como as frontais e temporais por exemplo, uma menor idade e duração de epilepsia no momento da cirurgia demonstraram ser fatores preditivos de bom prognóstico (43, 44). Além disso, uma idade inferior a 18 anos no momento da cirurgia parece ser fator preditivo positivo independente para melhora nas atividades diárias de vida, satisfação familiar, ajuste psicossocial e melhora na qualidade de vida global (36, 45, 46).

Em todos os pacientes submetidos ao procedimento, descargas epilépticas permanecem no EEG pós operatório, mostrando que a calosotomia não suprime a atividade epilética. Porém, os ritmos de base tendem a ser mais organizados e este achado tende a aparecer concomitantemente com uma melhora da performance psicossocial, significando uma melhora da qualidade de vida (36, 47). A secção do caloso diminui o desenvolvimento de atividade elétrica bissincrônica, lateraliza e reduz a frequência e duração das descargas ictais (36, 39, 47). Alguns estudos mostraram que a diminuição da atividade epilética bissincrônica parece também ser fator de bom prognóstico (36, 47). A restrição da atividade elétrica anormal a um hemisfério pode facilitar o controle medicamentoso da epilepsia e proporcionar ao paciente uma vida livre de crises.

Outras modalidades terapêuticas como a dieta cetogênica e o canabidiol também são opções terapêuticas para epilepsias de difícil controle, porém não específicas para crises de queda (48). Nos últimos 15 anos, a estimulação do nervo vago (VNS), têm sido usada como tratamento de primeira linha para uma variedade de sindromes epiléticas medicamente intratáveis (49). Entretanto, em uma revisão sistemática, quando comparada à VNS, a calosotomia demonstrou ser muito superior independentemente da extensão (12). Conforme este estudo, a calosotomia conseguiu um índice de redução nas crises de drop attack de mais de 50% em 85,6% dos pacientes contra 57,6% no grupo submetido ao VNS. Eventos adversos também foram mais frequentes no grupo submetidos ao VNS (22% vs 3,2%). A evidência disponível sugere que a calosotomia é potencialmente mais efetiva que a estimulação do nervo vago em reduzir drop attacks e crises generalizadas. Além disso a relação do custo benefício (especialmente em países em desenvolvimento) é melhor em favor da calosotomias, já que esta não requere o uso de um estimulador de alto custo. Um estudo relata uma melhora substancial em pacientes submetidos à calosotomia anterior em uso de estimulador de nervo vago. Todavia, não fica claro se estes resultados se devem ao uso do estimulador, à cirurgia ou ambos (15).

Historicamente, a calosotomia era realiza a seccionando porção anterior do corpo caloso, pois a maioria dos pacientes apresentava bissincronia das regiões anteriores do cérebro no EEG e também por se pensar que as fibras comissurais da região motora (que provocariam as crises de atonia), cruzavam para o hemisfério contralateral na metade anterior do corpo caloso (30). Este modelo de sintopia foi amplamente aceito até que estudos com ferramentas mais modernas (RNM com DTI) demonstraram uma sintopia mais posterior dos feixes motores na organização topográfica do corpo caloso (19, 20, 28, 31, 42).

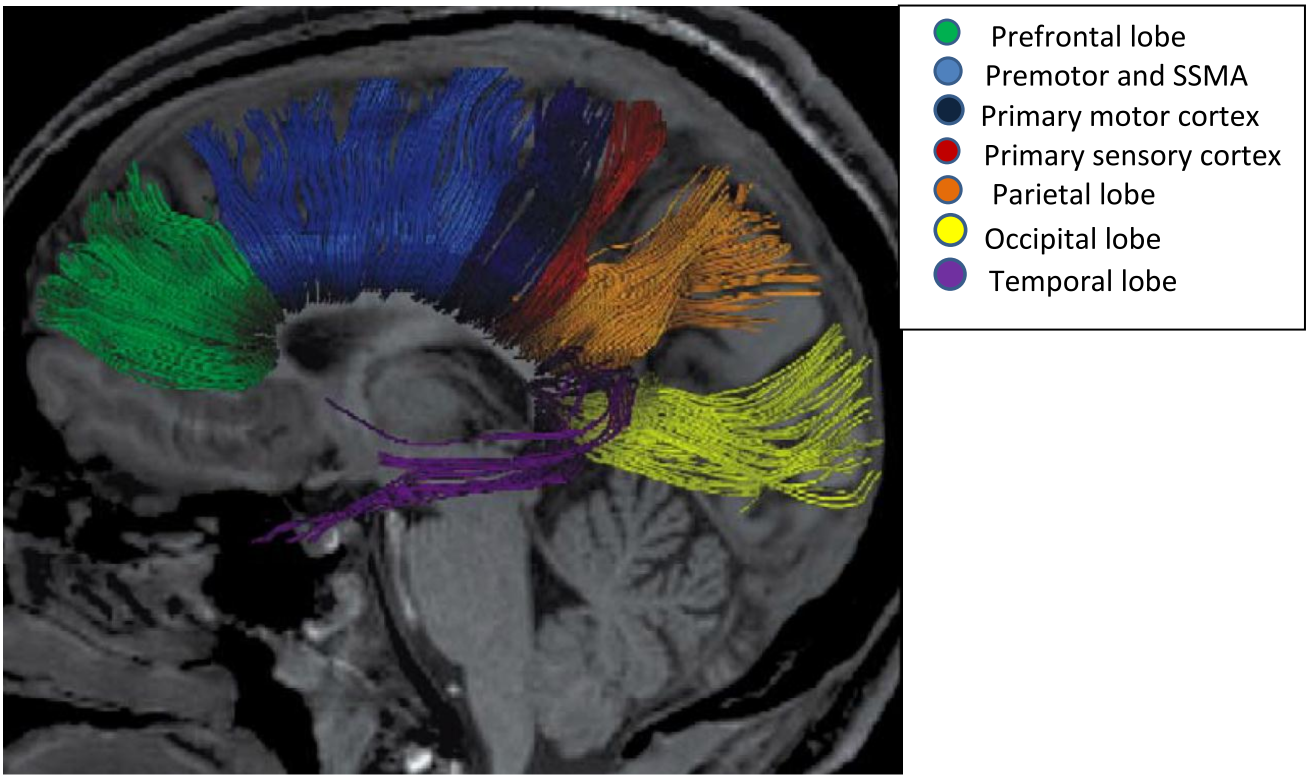


Fig 8. Tractografia demonstrando a sintopia das fibras calosas na linha média.(20)

Muitos pacientes que não apresentavam uma melhora significativa após a ressecção anterior do corpo caloso eram submetidas a uma ressecção complementar da porção posterior. Inclusive o grupo do hospital Glostrup na Dinamarca, usava esta estratégia cirúrgica como rotina (38). Pacientes com anormalidades cerebrais difusas nunca obtinham um bom resultado cirúrgico com a calosotomia parcial anterior e invariavelmente precisavam da complementação posterior para atingir um bom controle das crises (7). Em 2007, Scott et al publicaram uma série de pacientes pediátricos onde demonstraram uma redução de 75% das crises no grupo submetido à calosotomia total comparado a uma redução de 55% no grupo que realizou a calosotomia anterior. Além disso, a satisfação familiar com o procedimento foi de 89% e 73% respectivamente. Ali et al reportam que quanto maior a extensão da cirurgia melhor o resultado na redução de drop atacks e crises generalizadas. Outro estudo mostra uma redução de 94% nas crises de atonia no grupo submetido a calosotomia total contra 65% no grupo submetido a calosotomia anterior (45). Spencer publicou em 1988 que 77% dos pacientes se beneficiaram após a calosotomia total enquanto apenas 35% se beneficiaram da secção parcial. Mais recentemente, Pinard relatou que a calosotomia anterior para tratar crises de drop attack em pacientes com sindrome de West só foi efetiva em 27% das crianças, enquanto a calosotomia total foi efetiva em 89% delas. Diversos outros estudos relataram resultados semelhantes onde pacientes submetidos a calosotomia que incluía a porção posterior do corpo caloso tiveram resultados significativamente superiores quando comparados ao grupo submetido a desconexão apenas da metade ou dois terços anteriores (5, 6, 8, 9, 11, 14, 15, 36, 50). Somado a isto, Sunaga publicou em 2009 um trabalho relatando um baixo índice de recorrência de drop attacks depois de realizada uma calosotomia, mas que este índice só poderia ser atribuído ao grupo de pacientes submetidos a uma calosotomia total (5). Alguns autores advogam que a calosotomia total deve suceder a anterior em caso de falha terapêutica. Em um estudo publicado em 2009 no journal of Neurosurgery, o autor relata uma melhora de 75% naqueles pacientes submetidos à complementação posterior da calosotomia (4). Ou seja, a vasta maioria destes pacientes apresentavam uma melhora substancial do número e intensidade das crises epiléticas após a complementação posterior, especialmente as do tipo atônicas. Logo, quando a secção anterior do corpo caloso falhava em controlar as crises de drop attack, a extensão posterior para calosotomia total melhoravam consistentemente os resultados (5, 6, 36, 40, 45). Hipotetizamos assim que, em casos onde há a indicação do procedimento, uma ressecção seletiva da porção posterior poderia ser considerada como procedimento inicial, e que os bons resultados da desconecção completa seriam na verdade, resultado da ressecção posterior. Esta teoria veio a ser corroborada tanto por dados anatômicos e radiológicos quanto por resultados cirúrgicos (13, 19, 20, 31, 51). Estudos mais recentes com tecnologias mais modernas (RNM com DTI) mostraram que as fibras calosas que interconectam as áreas motoras homólogas, passam pelo corpo caloso em áreas muito mais posteriores do que se achava anteriormente quebrando assim uma paradigma de anos (19, 20, 31). Fig. 9, 10, 11. Evidências disponíveis mostram uma organização topográfica constante em seres humanos (19).

“The mapping of callosal radiation, by which corresponding cortical areas of opposites hemispheres are connected, was achieved in detail and, for example, accounts for a clear separation of callosal primary motor and sensory fiber bundles. Most importantly, however, fibers originating in the motor cortex were found to cross the corpus callosum through its posterior half.”

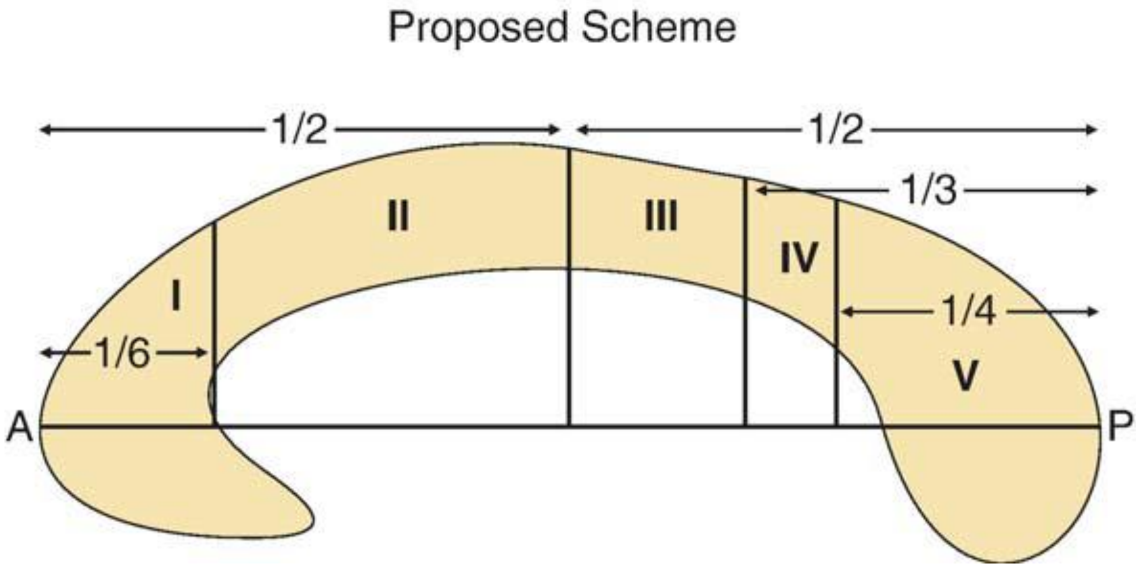


Fig 9. Nova classificação proposta para sintopia da fibras no corpo caloso. Region I: prefrontal; region II: premotor and
supplementary motor; region III: motor; region IV: sensory; region V:
parietal, temporal, and occipital. A, anterior; P, posterior.(20)

"Fibers arising from the sensory-motor cortex pass through the isthmus. Sensory and motor stimulation rarely activated foci in the middle anterior area but have been elicited in the posterior Corpus Callosum."

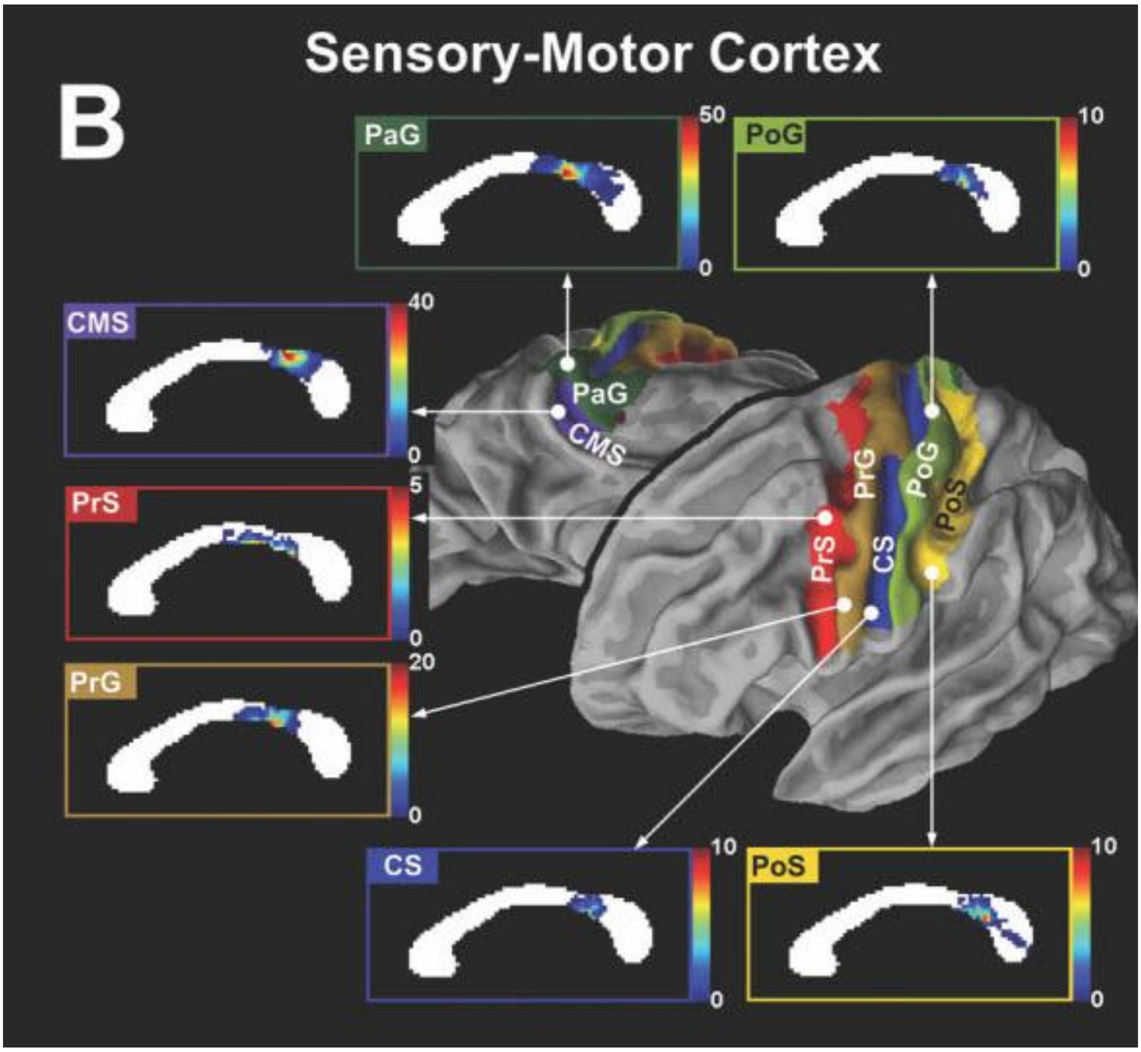


Fig 10. Conexões do corpo caloso. Maps of the interhemispheric sensory-motor cortex were derived from the cingulated sulcus marginalis region (CMS), paracentral gyrus (PaG), precentral gyrus (PrG), precentral sulcus (PrS), central sulcus (CS), postcentral sulcus (PoS), and postcentral gyrus (PoG). Callosal connection maps were also derived from the parietal cortex, including the precuneus gyrus (PcG), parieto-occipital sulcus (POS),subparietal sulcus (SPS), parietal superior gyrus (PSG), intraparietal and parietal transverse sulcus (IPS), and parietal inferior gyrus angular part (IAG). Connection maps of cingulated gyrus (CGG) and cingulate sulcus (CGS) are also shown.(31)

“Our map located primary motor and somatosensory tracts in the midbody of the CC.”

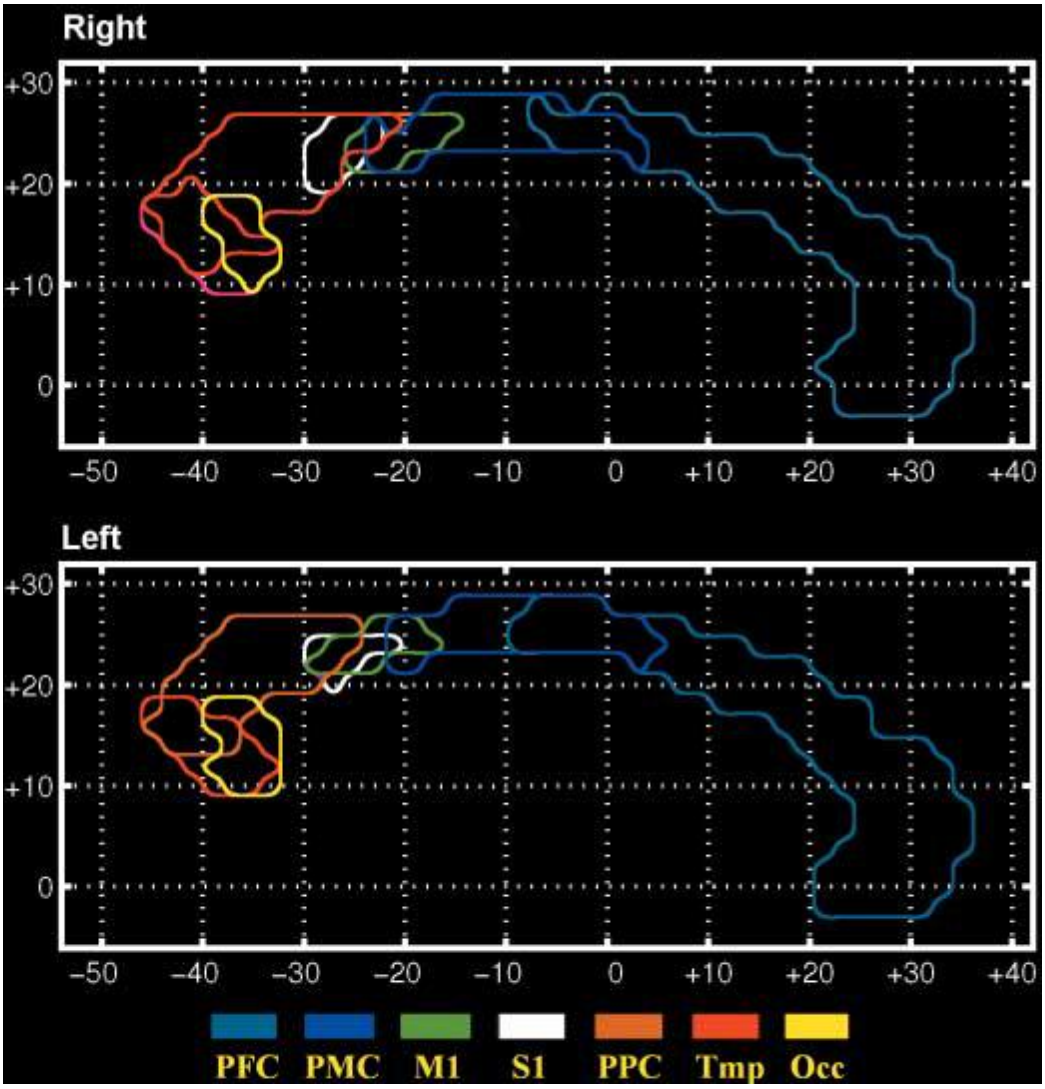


Fig 11. Mapa de 7 regiões no corpo caloso na altura da linha média. Results for tracking to targets in the right hemisphere are shown at the top, and for the left hemisphere at the bottom. Abbreviations: PFC, prefrontal; M1, primary motor; S1, primary somatosensory; PPC, posterior parietal; PMC, premotor; Occ, occipital; Tmp, temporal.(19)

Além disso, técnicas microscópicas identificaram axônios com maior diâmetro passando pelo corpo e istmo do corpo caloso (fig. 12), justamente na topografia das fibras motoras, significando uma maior velocidade de condução, ocasionando assim uma rápida propagação da descarga epiléptica e desenvolvimento eletroencefalográfico de atividade bissincrônica (20, 21, 42).

"…larger diameter fibers interconnect primary sensory and motor areas than association and prefrontal areas. The region with the highest density of large callosal fibers is the posterior midbody."

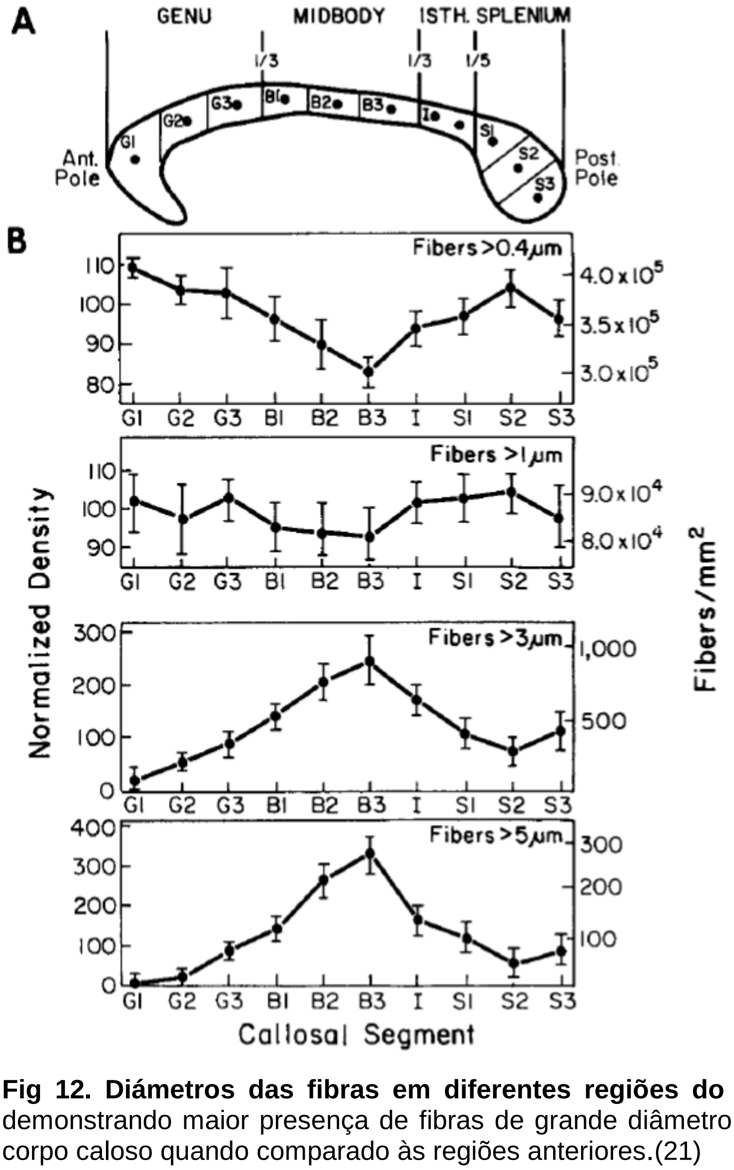
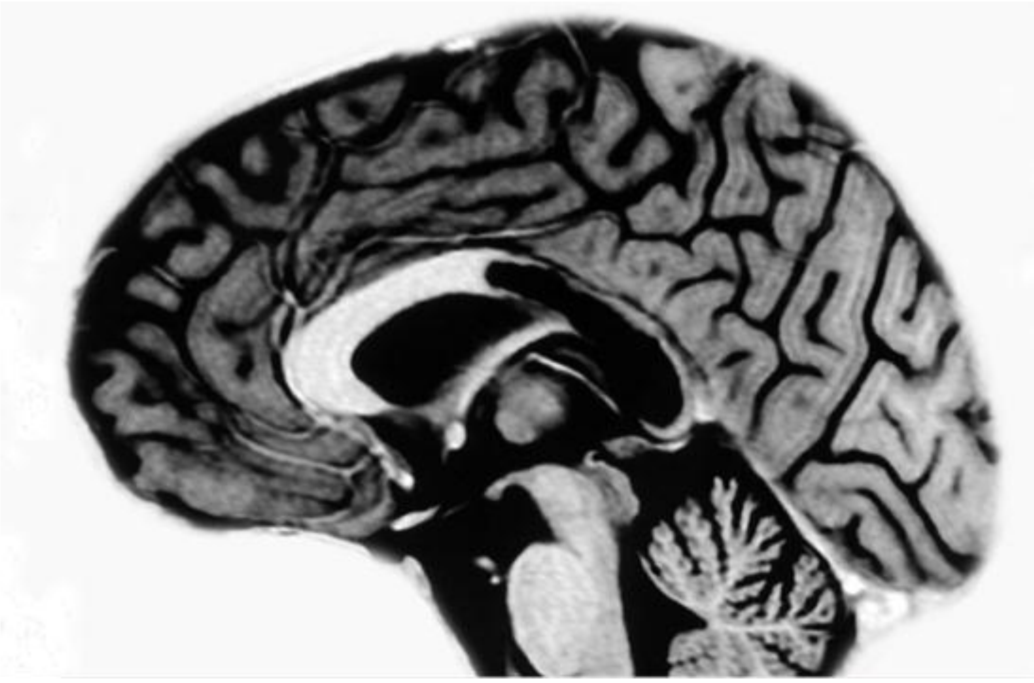


Fig 12. Diámetros das fibras em diferentes regiões do corpo caloso. Esquema gráfico demonstrando maior presença de fibras de grande diâmetro na porção posterior do corpo do corpo caloso quando comparado às regiões anteriores.(21)

Alguma relutância em seccionar a porção posterior do corpo caloso foi ao longo dos anos descrita na literatura por teoricamente causar uma síndrome de desconexão (3, 4, 6, 8, 9, 52). O córtex de associação posterior modula a linguagem e as habilidades espaciais e visuais, integração esta que transita pelas fibras do caloso posterior. Entretanto, não é bem claro o quão relevante esta síndrome (sempre transitória), é em pacientes com disfunção cerebral severa e crises de atonia, e mesmo em pacientes com cognição razoável, esta sindrome é, na maioria dos casos só detectada através de testes específicos (36). Na prática clínica, a sindrome de desconexão pós calosotomia é raramente vista e em pacientes pré puberes ou mais jovens há uma substancial melhora cognitiva (7). Apatia transitória no pós operatório provavelmente é relacionada e ocorre em casos de desconecção da convexidade e da porção mesial do lobo frontal anterior (36). Este evento não ocorre na calosotomia posterior seletiva já que as fibras frontais mais anteriores são sempre poupadas (13). Hemiparesia também tem sido descrita na literatura tanto nos pacientes submetidos à calosotomia total quanto nos submetidos à calosotomia anterior (18), podendo ocorrer devido ao afastamento da área motora contralateral ou também pela coagulação de veias corticais com o objetivo de atingir a fissura interhemisférica. Esta complicação não ocorre na técnica posterior seletiva já que o acesso cirúrgico ocorre longe da área motora (mais posterior) e numa área cortical onde raramente há grandes veias de drenagem para o seio sagital superior (25, 26). Estudos recentes vem demonstrando que a ressecção da porção posterior do corpo caloso é segura no que diz respeito a sindrome de desconexão e deficits neurológicos e que o procedimento inclusive melhora a atenção, comportamento e autonomia dos pacientes (13, 14, 53). Em outras palavras, a sucessão de crises epiléticas severas e recorrentes, parece causar um malefício maior do que a própria síndrome em questão, e por este motivo, ela não deve ser fator impeditivo ao procedimento (10, 54-56).

No programa de cirurgia da epilepsia de Porto Alegre - Hospital São Lucas da PUCRS, os pacientes candidatos ao procedimento, são submetidos a uma ressecção seletiva dos dois terços posteriores do corpo caloso. Temos obtido melhora clínica significativa, com diminuição drástica ou cessação das crises de atonia (queda ao solo) e também no número e intensidade de outros tipos de crises epilépticas generalizadas. Além da redução das crises, o procedimento geralmente resulta numa melhora comportamental e de nível de atenção dos pacientes, assim como uma satisfacao dos pais e/ou cuidadores. A primeira série de 36 pacientes foi publicada em 2016 com resultados animadores tanto no controle de crises de atonia (quando analisamos as crises de atonia as informações dos familiares são fidedignas por se tratar de manifestação muito particular e evidente se comparadas com alguns outros tipos de crises), quanto na melhora global da qualidade de vida dos pacientes. Os resultados foram semelhantes às séries históricas de calosotomia total, sugerindo assim que as fibras calosas anteriores podem ser poupadas. Apesar dos bons resultados, a calosotomia posterior seletiva não foi completamente efetiva em cerca de 20% dos pacientes, sugerindo que há uma série de fatores heterogêneos que levam às quedas (13). Este subgrupo de pacientes apresentou uma redução não tão expressiva na frequência de *drop attacks*.

O timing e a extensão da calosotomia para se obter os melhores resultados com mínimo risco é ainda controverso (6). A maioria das publicações são estudos retrospectivos de centros únicos (exceto metanálises) e nenhum deles descreve resultados e fatores prognósticos das calosotomias posteriores seletivas. Diferentes estudos descrevem fatores prognósticos nos pacientes submetidos a calosotomia (5, 11, 16-18, 36, 50). Reutens descreve um pior prognóstico nos pacientes com grave comprometimento cognitivo e atividade epiléptica independente bilateral no EEG (11). Em uma metanálise publicada em 2018, Alvin descreve como favoráveis para um bom desfecho clínico, as seguintes características: RNM sem alterações estruturais, curta duração da epilepsia, calosotomia total, epilepsia idiopática sobre etiologia conhecida (16). Todos os estudos que relatam fatores preditivos falam apenas sobre calosotomia anterior ou total. Assim, este é um trabalho original já que apresenta dados prognósticos relacionados à pacientes submetidos à calosotomia posterior seletiva. Entender o valor preditivo de variáveis nos pacientes submetidos a este procedimento específico será benéfico no planejamento cirúrgico, seleção e aconselhamento dos pacientes candidatos ao tratamento. Neste estudo, buscamos correlacionar fatores e características pré-operatórias (idade na cirurgia, duração da epilepsia, idade de início das crises e etiologia), assim como exames pós operatórios (RNM com tractografia) com os resultados dos pacientes submetidos a calosotomia posterior seletiva quanto ao controle das crises de atonia (drop attacks) descrevendo assim, achados até então inéditos na literatura médica.



B

Fig 13. RNM pós operatótria demonstrando a ressecção da porção posterior do corpo caloso.

2 JUSTIFICATIVA

As epilepsias de difícil controle (refratárias) constituem uma condição extremamente grave, representando uma verdadeira catástrofe social. A vida do paciente assim como o dia-dia dos que o cercam fica voltada para a doença e os cuidados que o paciente portador demanda. O conceito de “burden of disease” (*ônus da doença; impacto de um problema de saúde, medido pelo custo financeiro, mortalidade, morbidade ou outros indicadores*) fica nesta situação, muito bem exemplificado.

Além disso, os pacientes que sofrem de crises de atonia, apresentam grande risco de sofrerem graves traumatismos e até mesmo de morte durante um ataque. Não raramente estes pacientes se apresentam com muitas cicatrizes e um histórico de diversas internações por traumatismo craniano e facial (Fig14).

Fig 14. Exemplos de pacientes submetidos à calosotomia posterior seletiva que apresentavam múltiplas cicatrizes no escalpo decorrentes de repetidos traumas precedidos de crises de queda.

Pacientes com crises súbitas de queda ao solo submetidos à calosotomia posterior seletiva apresentam grande melhora na qualidade de vida em geral. Soma-se a isto a diminuição dramática de lesões graves decorrentes das quedas. Um paciente com epilepsia bem controlada tem melhores chances de independência e deixando assim de ser um pesado fardo para seus respectivos cuidadores.

Existe porém, um pequeno grupo de pacientes que não tem uma melhora tão significativa. Pelos motivos expostos acima, é de suma importância que compreendamos os motivos pelos quais isto acontece e o que podemos fazer para evitar um desfecho menos favorável além de melhorar a seleção dos pacientes candidatos ao procedimento.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Descrever resultados cirúrgicos e definir e fatores associados a um bom outcome clínico no que se refere ao controle das crises de drop attack (quedas súbitas ao solo) em pacientes submetidos à calosotomia posterior seletiva.

3.2 OBJETIVOS ESPECÍFICOS

1. Determinar se a extensão da ressecção do corpo caloso tem uma influência favorável na melhora das crises de queda.
2. Correlacionar a persistência de fibras do corpo caloso oriundas das regiões motoras e pré motoras com a continuidade de crises epiléticas do tipo drop attack no pós operatório.
3. Determinar se a idade do paciente no momento da cirurgia é fator prognóstico importante.
4. Determinar se a duração da epilepsia no momento da cirurgia está relacionado a um bom controle dos drop attacks.
5. Determinar se a etiologia da epilepsia tem relação com bom controle pós operatório dos drop attacks.

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5 ARTIGO ORIGINAL

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Control of Drop Attacks with Selective Posterior Callosotomy: Anatomical and Prognostic Data*

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ABSTRACT

Objective: In a previous proof of concept study, selective posterior callosotomy achieved similar degree of control of drop attacks as total callosotomy, while sparing prefrontal interconnectivity. The present study aims to confirm this finding in a larger cohort and to provide anatomical and prognostic data.

Methods: Fifty-one patients with refractory drop attacks had selective posterior callosotomy and prospective follow up for a mean of 6.4 years. Twenty-seven patients had post-operative magnetic resonance imaging (MRI) and 18 had tractography (DTI) of remaining callosal fibers. Pre and postoperative falls were quantified and correlated with demographic, clinical and imaging data.

Results: Median monthly frequency of drop attacks decreased from 120 to 0. Forty- one patients had either complete or greater than 90% control of the epileptic falls. Age and duration of epilepsy at surgery correlated with outcome (p values, respectively, 0.042 and 0.005). Mean index of callosal section along the posterior-to-anterior axis was 53.5%. Extending the posterior section anterior to the midbody of the corpus callosum did not correlate with seizure control (p 0.91), providing fibers interconnecting the primary motor (M1) and caudal supplementary motor area (SMA) were sectioned. Only one patient had a notable surgical complication which resolved in two days.

Conclusions: This level III cohort study with objective outcome assessment confirms that selective posterior callosotomy is safe and effective to control epileptic falls. Younger patients with smaller duration of epilepsy have better results. A posterior section contemplating the splenium, isthmus and posterior midbody seems sufficient to achieve complete or almost complete control of drop attacks.

Key words: Corpus Callosum, Epilepsy Surgery, Selective Posterior Callosotomy.

INTRODUCTION

The corpus callosum (CC), with more than 200 million transverse axonal projections, is the largest bundle of commissural fibers in the human brain, accounting for 70-80% of the connection between the cerebral hemispheres (1-4). It is widely accepted that rapid spread and bilateral synchronization of ictal discharges through the CC in patients with severe epilepsies is related to epileptic drop attacks and that corpus callosotomy is a plausible treatment option when these seizures are refractory to antiepileptic treatment [5-17].

In most centers, corpus callosotomy is performed by sectioning variable extents of the anterior portion of the corpus callosum, and often transformed into a more efficacious total disconnection when patients fail the initial procedure[6, 8-10, 13, 15, 18, 19-21]. This ‘anterior-first’ approach has been preferred due to the predominance of bisynchronous electroencephalogram (EEG) discharges in the anterior head regions and also because it has traditionally been thought that the callosal fibers interconnecting the premotor and the primary motor cortex cross in the anterior half of the CC [22]. Recently, however, modern imaging and brain dissection techniques have challenged this anatomical view, showing that callosal fibers originating in primary motor cortex cross more posteriorly, between the body and the splenium [1-3, 23, 24].

We recently reported 36 patients in whom we performed selective posterior callosotomy, disconnecting the posterior half of the CC and sparing prefrontal connectivity. Results were similar to total callosotomy and we hence posited that the significantly better results seen with total in comparison to anterior callosotomies had to do with the disconnection of the fibers originating in premotor and primary motor cortices that cross in the posterior half of the CC, rather than to a complete disconnection of the CC per se. The significant post-operative improvement of overall daily functioning in our patients suggests that it is probably relevant to spare the connectivity between the frontal lobes [12].

In spite of complete or almost complete control of drop attacks in 80% of patients, selective posterior callosotomy did not provide similar results for 1 in 5 patients, and we failed to find predictors of response to the procedure. In regard to anterior or total callosotomies, a recent metanalysis showed that MRI without structural changes, a short duration of epilepsy, total disconnection, and idiopathic epilepsy over known etiology predicted better results [15]. Similar data regarding selective posterior callosotomy is nonexistent.

Here we report an extension of the series to 51 consecutive patients with disabling drop attacks who had selective posterior callosotomy and correlate demographic and imaging variables with control of drop attacks. We have refined the imaging analyses in half the sample using MRI and tractography (DTI) to study the extent of callosal resection. We hypothesized that section of the fibers originating in M1 and caudal SMA (‘executive’) areas would be necessary and sufficient to provide significant control of drop attacks and that a larger series of patients would provide meaningful correlations and predictions regarding control of falls.

METHODS

This prospective cohort study providing Class III evidence reports a large series of patients with severe epilepsies presenting frequent, refractory epileptic drop attacks, operated according to a novel callosotomy strategy, in which the posterior half of the CC is sectioned, sparing prefrontal interconnectivity [14]. Surgical outcome, demographic and epileptologic features and postoperative imaging were analyzed and correlated with degree of control of drop attacks. Data was collected during regular management of patients with severe epilepsies at the Porto Alegre Epilepsy Surgery Program, Hospital São Lucas, PUCRS.

The procedure was detailed to patients and relatives, and particularly risks, possible complications, and realistic perspectives of clinical and functional outcomes were emphasized. It was explained that although not a routine examination, postoperative MRI after a minimum of 6 months of follow up would be offered. Because virtually all patients had intellectual disability, written informed consent was signed by relatives. The study was approved by the institutional ethics committee, protocol number 2.612.300.

From April 1997 to March 2018, 51 patients with severe multifocal epilepsies and epileptic encephalopathies presenting refractory drop attacks as the main disabling seizure type underwent presurgical evaluation and selective posterior callosotomy at the Porto Alegre Epilepsy Surgery Program. Thirty-one were male. Mean (range; SD) age at seizure onset, age at surgery and epilepsy duration were, respectively, 4 (0-40; 6.57; median 1); 20 (5 – 56; 12.2; median 21) and 17 (2-50; 11.4; median 16) years. Mean follow-up was 6.4 years (range, 1 - 17.5; SD 4.6; median 4.7).

Patients were included based on the presence of sudden refractory drop attacks, regardless of the etiology of epilepsy, providing (i) it was possible to record at least one atonic or tonic seizure during video-electroencephalographic monitoring, (ii) EEG showed intense bi-synchronous generalized epileptic discharges as seen in epileptic encephalopathies, (iii) correlation between EEG and MRI did not identify a resectable epileptic focus, and (iv) at least 6 months of post-operative follow up was available and results were verified through direct contact with relatives. Intellectual disability was the norm and thus, not a reason for exclusion.

Twenty-four patients had epilepsy of unknown etiology, 13 had hypoxic ischemic perinatal lesions, 3 bilateral perisylvian polymicrogyria, 3 lyssencephaly, 1 bilateral periventricular heterotopia, 1 unilateral periventricular heterotopia, 2 sequelae of prematurity, 1 sequelae of encephalitis, 1 encephalopathy due to radiotherapy, 1 sequelae of cranial trauma and 1 tuberous sclerosis.

Four patients in whom follow up was not directly available from examination at the epilepsy surgery outpatient clinic nor through a structured telephone interview contact were excluded. In addition to drop attacks, all patients had other seizure types. However, only the frequency of drop attacks was considered because (i) these are extremely debilitating seizures with imminent risk of trauma and need for constant supervision, (ii) they can be easily identified thus facilitating quantification, and (iii) because their control is the main objective of selective posterior callosotomy.

Interictal prolonged video-EEG recordings determined whether discharges were generalized, multifocal, or significantly lateralized. Ictal recordings were analyzed to assure that tonic or atonic seizures involved sudden diffuse attenuation or generalized spike or polyspike-slow wave patterns. Preoperative MRI in patients 1-36 (table 1) was in a 1.5T Siemens machine (Siemens AG, Erlangen, Germany) whereas in patients 37-51 (table 1) in a GE Healthcare device (GoldSeal Signa HDx General Eletric, Milwaukee, WI).

Post-operative MRI (all in the 3.0 T magnet) was performed in 27 patients who both have given informed consent and lived in the Porto Alegre geographic area. We hypothesized that significant control of atonic and tonic seizures needed sectioning the callosal fibers originating from M1 and the pre-motor area (PMA), including those associated with negative motor phenomena [1, 14, 22, 25-27]. To achieve this goal, roughly 50% (the posterior half) of the CC should be disconnected, sparing fibers that interconnect the pre-frontal cortex. As a corollary, we reasoned that patients who did not show significant improvement in control of drop attacks would have had smaller callosal resections. We calculated the extension of the CC resection measuring the distance between the anterior limit of the genu to the posterior portion of the splenium (variable X). The sectioned portion of the corpus callosum was measured from the anterior margin of the section to the posterior portion of the splenium (variable Y). This ratio (Y / X), is illustrated in figure 1. All measurements were done electronically in the Arya version 3.3 (tool for visualization, interpretation and manipulation of medical images in DICOM format, from diagnostic imaging equipment) by the same examiner (T.F.). In 18 of these 27 patients it was possible to perform tractography of the remaining callosal fibers using Mrtrix software, which provides a series of tools to perform diffusion analysis in MRI data. All images were converted to NifTi and preprocessed with FSL software [https://fsl.fmrib.ox.ac.uk/fsl/fslwiki] and

MRTRIX [http://www.mrtrix.org/]. Then, images were corrected for motion artifacts [28] and fiber orientation distribution maps were generated with the MRTrix spherical deconvolution algorithm [29] using factor of 6 as maximum harmonic order. The generation of the tract for each patient was performed by an experienced neuroradiologist (R.B.S), using the tool based on spherical regions of the MRTrix and the algorithm of Second Order Integration on Fiber Orientation Distributions [30] (iFOD2) (fig2). In these patients, the persistence of fibers interconnecting the homologous M1 and PMA was analyzed. These findings were compared with the drop attack control, in order to determine if the presence of these residual fibers correlates with a better or poorer outcome. In order to define the presence of these fibers, ROIs (regions of interest) of approximately 1cm length were applied in the most distal portion of the remaining corpus callosum after surgery. Accurate images of the remaining fibers were then obtained and the brain cortical areas where these bundles ended were registered.

All were stabilized on a combination of valproate, lamotrigine, and a benzodiazepine after operation, as this regimen has proved effective in control of drop attacks. Doses were allowed to change over the years, according to occasional relapses or side effects.

Pre-operatively, relatives were instructed to keep a diary of drop attacks. We used the frequency of the 3 months before operation to calculate baseline frequency and compared with the information after operation. The frequency of falls was quantified as number of drop attacks/month. Atonic seizures that occurred with patients seated, lying down or protected were also recorded.

Patients were classified in **3 groups**: free from drop attacks (i), reduction ≥ 90% in the frequency of falls (ii), reduction < 90% in the frequency of falls (iii). Groups 1 and 2 were considered as having highly favorable results and group 3, an unfavorable result.

Demographic correlations

Age at seizure onset, age at surgery, duration of epilepsy before operation and etiology were correlated with degree of control of drop attacks. We subdivided age at surgery and duration of epilepsy in 0 to 30 years and 31 or more years.

Quantitative data related to frequency of drop attacks were described by median (IQR interquartile range) and mean (minimum and maximum values). Categorical data were presented by absolute numbers and percentages. Pre and post op frequency of drop attacks was compared using Wilcoxon T test (signed rank test). Additionally, the percent change in drop attacks frequency was calculated according to the formula: ((final value - initial value) / initial value) * 100 * -1).

Association between the extent of section of the corpus callosum and post-op frequency of drop attacks was evaluated by the Spearman correlation coefficient. Mean rates were compared between the 2 age groups by the oneway ANOVA test with a robust standard error (Welch's test), followed by a post-hoc T3 from Dunnett. Pearson's correlation index was used to determine association of age at surgery and duration of epilepsy with drop attacks control. A multivariate analysis was performed, with reduction in frequency of drop attacks as the dependent variable and age and duration of epilepsy at surgery, age at seizure onset, etiology, preoperative monthly frequency of drop attacks and extent of callosal resection as independent variables, p values <0.20 were considered significant. The data was analyzed with SPSS software version 22.0.

RESULTS

Control of drop attacks

Median and mean monthly frequency of drop attacks before surgery were respectively 120 (Interquartile range - IQR: 240) and 297 (min 5 - max 3,000; SD 537) and reduced to a median of 0 (IQR: 3) and a mean of 16 (min 0 - max 150; SD 39.2). On average, the overall reduction in the frequency of drop attacks was 89.3%. Twenty-eight patients (55%) achieved complete control of the falls, often following a running down course over two to three months, in parallel with adjustment of antiepileptic medications. Thirteen of the remaining 23 (25.4%) had a more than 90% reduction in falls. Thus, 41 of 51 patients (80,3%) had complete remission or a higher than 90% reduction in the frequency of drop attacks, and only 10 patients (19,7%) did not achieve significant improvement after selective posterior callosotomy.

In the 41 patients who had complete or almost complete control of falls, pre-operative frequency was on average 120% higher when compared to the group of patients who did not improve. However, frequency of drop attacks prior to surgery did not correlate with control of drop attacks after callosotomy (p = 0.13).Seizure outcome of all patients are shown in table 1.

Table 1. Demographic data of 51 consecutive patients (DA* (drop attacks/month))

Patient	Age at Surgery	Epilepsy Duration	Etiology	Pre-op DA*	Post-op DA*	% Reduction	Callosal section index %
APM	20	20	Unknown	700,0	0,0	100,00	37,61
ASP	27	16	hypoxic ischemic perinatal lesions	300,0	90,0	70,00	N/A
ACG	12	12	hypoxic ischemic perinatal lesions	60,0	0,5	99,17	60,30
APC	9	9	Unknown	12,0	0,0	100,00	N/A
BZA	17	13	Unknown	50,0	0,0	100,00	39,48
CS	30	20	Bilateral perisylvian polymicrogyria	20,0	0,0	100,00	39,52
CTD	28	28	Prematurity	90,0	0,0	100,00	N/A
CF	11	5	Unknown	1500,0	0,0	100,00	N/A
CG	43	43	hypoxic ischemic perinatal lesions	150,0	120,0	20,00	N/A
CFD	29	19	Unknown	60,0	0,0	100,00	88,62
CSO	15	15	Tuberous Sclerosis	300,0	0,0	100,00	59,67
DFS	7	7	Encephalitis	150,0	150,0	0,00	44,82
ELM	15	8	Unknown	150,0	2,0	98,67	N/A
EJB	24	20	Bilateral perisylvian polymicrogyria	300,0	0,0	100,00	48,82
EBS	12	12	Unknown	180,0	0,0	100,00	N/A
ET	5	2	Unknown	300,0	0,0	100,00	47,14
FLA	24	19	Unknown	30,0	1,0	96,67	N/A

FPS	12	11	Lyssencephaly	300,0	0,0	100,00	N/A
GLM	28	28	Trauma	90,0	2,0	97,78	64,19
GMS	32	27	Unknown	150,0	0,0	100,00	N/A
GL	29	26	Unknown	8,0	0,0	100,00	62,88
GBM	40	39	hypoxic ischemic perinatal lesions	5,0	3,0	40,00	58,44
HFR	12	9	Encephalopaty due to radiotherapy	180,0	60,0	66,67	33,92
HMS	24	18	hypoxic ischemic perinatal lesions	180,0	0,5	99,72	N/A
IFR	13	13	hypoxic ischemic perinatal lesions	90,0	0,0	100,00	N/A
JFS	23	19	Bilateral periventricular heterotopia	12,0	6,0	50,00	52,87
JT	35	31	Unknown	40,0	12,0	70,00	67,27
JLS	20	20	hypoxic ischemic perinatal lesions	120,0	0,0	100,00	48,25
JAPV	19	4	hypoxic ischemic perinatal lesions	480,0	0,0	100,00	N/A
KVP	21	21	hypoxic ischemic perinatal lesions	300,0	150,0	50,00	70,53
LVE	6	6	Unknown	3000,0	0,0	100,00	49,77
LVBA	28	21	hypoxic ischemic perinatal lesions	210,0	0,0	100,00	N/A
LPS	15	14	Lyssencephaly	60,0	4,0	93,33	N/A
LCDG	21	21	Unknown	140,0	0,5	99,64	N/A
LSA	16	16	Unilateral periventricular heterotopia	60,0	0,0	100,00	56,43
MPE	29	13	Unknown	120,0	60,0	100,00	50,45
MGB	56	50	hypoxic ischemic perinatal lesions	5,0	0,0	50,00	43,36
MJP	20	14	Unknown	120,0	0,0	100,00	62,55
MMN	30	29	Lyssencephaly	90,0	0,5	99,44	N/A
MCS	21	21	Unknown	120,0	32,0	73,33	65,35
NLS	6	6	Unknown	2000,0	0,0	100,00	41,73
PMPL	17	16	Unknown	60,0	1,0	98,33	N/A
RA	13	7	Unknown	120,0	0,5	99,58	N/A
RRM	15	7	Unknown	60,0	0,0	100,00	N/A
RNR	46	6	Prematurity	450,0	12,0	97,33	47,15
TM	15	6	hypoxic ischemic perinatal lesions	1200,0	120,0	90,00	51,81
TRB	17	16	Unknown	180,0	0,0	100,00	N/A
TJL	24	18	Unknown	100,0	0,0	100,00	51,70
VHR	5	4	Unknown	600,0	0,0	100,00	N/A
WH	21	17	Bilateral perisylvian	24,0	0,0	100,00	N/A

XT	29	28	polymicrogyria hypoxic ischemic perinatal lesions	150,0	1,0		99,33	N/A

Demographic and clinical variables related to surgical outcome

Forty-five patients were younger than 30 years and 6 were older. Despite the relatively small figures, age at surgery was significantly associated with control of epileptic falls (Pearson's correlation coefficient (r) -0.43 and p = 0.002). Mean reduction in the frequency of drop attacks was 92.9% (min 0 – max 100; SD 18.8), median 100 (IQR: 1.5) in younger and 62.8% (min 20 – max 40; SD 32.07), median 60 (IQR 63) in the older patients. A strong association between control of drop attacks and duration of epilepsy was also seen (Pearson correlation index (r) of -0.58, p <0.001). The 47 patients with less than 30 years of epilepsy had a mean reduction of 93.2% (min 0 – max 100, SD 18.5), median 100 (IQR 1.6), compared to a reduction of 45% (min 20 – max 70, SD 20.8), median 45 (IQR 40) in the frequency of drop attacks in those with more than 30 years of epilepsy. In contrast, age at seizure onset did not correlate with reduction of drop attacks (Pearson correlation index (r) -0.15, p = 0.30). There was no significant relationship type and presence of a given etiology and seizure control. The demographic data of each subject is described in Table 1.

Post operative MRI: Posterior section of the callosum and tractography of callosal fibers

Twenty-seven patients (53%) had postoperative MRI and measurement of the extent of the posterior section of the CC. The mean index of callosal section was 53.5% along the posterior-to-anterior axis (SD, 11.6; min 33.9% - max 88.6%). This index did not correlate with rate of control of drop attacks (Pearson correlation index -0.02, p = 0.91) as shown in figure 2 and table 1.

Eighteen patients had post-op tractography of remaining callosal fiber bundles. Twelve had complete control of falls, 8 of whom (66%) had residual fibers connecting homologous rostral SMA and PMA, but none had residual fibers interconnecting the caudal SMA or M1 (Fig 3). Two other patients had greater than 90% improvement, and in one residual fibers interconnecting the rostral supplementary and pre motor areas were seen. Finally, 4 patients had a less favorable outcome, one of whom had residual fibers interconnecting the rostral SMA and PMA. Individual data is given in table 2:

Table 2. Tractography data with anatomical specificity in motor regions: Residual fibers interconnecting homologous regions (M1, SMAc and SMAr)).

PATIENT	DA control	RESIDUAL CALOSAL FIBERS - DTI		
		SMA rostral	SMA caudal	M1
BA	100%	Yes	No	No
MJA	100%	Yes	No	No
CS	100%	No	No	No
CFD	100%	No	No	No
CSO	100%	No	No	No
APMJ	100%	Yes	No	No
JLSJ	100%	No	No	No
EDS	100%	Yes	No	No
NLS	100%	Yes	No	No
LVE	100%	Yes	No	No
TJL	100%	Yes	No	No
LSA	100%	Yes	No	No
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TM	90-99%	Yes	No	No
GM	90-99%	No	No	No
JFS	<90%	No	No	No
DS	<90%	Yes	No	No
JT	<90%	No	No	No
MCS	<90%	No	No	No

Multivariate analysis

Included in the multivariate analysis were those variables with p <0.20: age at surgery, duration of epilepsy, pre-operative drop attacks/month, age at seizure onset, etiology, index of callosal section. The first two remained significantly correlated with seizure outcome (p values, respectively, 0.042 and 0.005). The relationship between age at surgery, duration of epilepsy and outcome in regard to control of drop attacks is illustrated in figure 2.

Surgical complications

Death, permanent sensory or motor deficits, ataxia, sphincter dysfunction and language disturbances did not occur in this series. One patient was drowsy for 48 hours and then recovered. Fever in the first 3 post-operative days occurred in three patients, in whom the roof of the lateral ventricle was opened and resolved spontaneously. Finally, one patient had a small intracranial hematoma with no intracranial hypertension at the surgery site. He was somnolent for 2 days and recovered completely.

DISCUSSION

Patients suffering from refractory epilepsies with drop attacks have recurrent trauma, severe restrictions on their daily lives and require constant supervision. In a previous proof of concept report, selective posterior callosotomy sparing prefrontal interconnectivity led to complete or greater than 90% reduction in the frequency of sudden falls in more than 80% of patients, therefore appearing to be a highly effective procedure [14]. Here we extend the series to 51 patients followed prospectively and add new clinical and anatomical data providing a refinement of the prognostication of control of drop attacks with selective posterior callosotomy. We confirmed the effectiveness of this novel procedure and showed that younger patients with shorter epilepsy duration have the best results. Finally, we showed that at least 40% of the corpus callosum in the posterior-to-anterior axis should be disconnected, thus including the splenium, the isthmus and the posterior portion of the body. However, control of falls was not dependent upon extending the resection anterior to the midbody of the CC.

Although the traditional and most used approach, anterior corpus callosotomy usually fails to provide significant control of drop attacks [7, 15, 16] and patients are often considered for a second procedure, transforming an anterior in a total callosotomy. Results with the latter are usually much better [8, 9, 13, 15, 16, 20, 21] leading to the contention that total callosotomy is the most effective strategy to control epileptic falls. However, in our previous study we hypothesised that the improved outcome following transformation of an anterior in a total callosotomy was not related to the completeness of the callosal section per se, but rather to the section of the relevant posterior callosal fibers. That hypothesis was based upon a combination of imaging observations showing that lesions in the premotor and primary motor cortex were associated with thinning of the posterior callosum [14] and tractographic evidence that fibers originating in the dorsolateral and medial PMA (including SMA) and in M1 cross in the posterior half of the CC, more specifically in the isthmus, extending to the anterior border of the splenium [1, 2, 24]. Because bilateral epileptic synchronization of these motor regions is thought to lead to sudden, generalised atonic and tonic seizures through a fast conducting polysynaptic mechanism involving the brainstem and spinal cord [25], section of these fibers is probably crucial to successful control of drop attacks. Moreover, fibers with the largest diameter, and hence faster conduction, are located in the posterior portions of the corpus callosum, precisely in the topography of motor fibers, whereas the prefrontal fibers crossing in the anterior callosum are thinner, poorly myelinated and with slow conduction times [3].

It has been thought that larger callosal sections are associated with better control of atonic seizures [9, 13, 15, 20, 21]. In a seminal paper, Spencer and colleagues reported improvement in the control of drop attacks in 77% of patients with total versus in only 35% with anterior callosotomy [10], and in children after West syndrome, total section controlled falls in 89% compared to 27% when only the anterior callous was sectioned [31]. More recently, a systematic review showed that the probability of significant control of drop attacks is 3 times higher with total than with anterior callosotomy [15]. Complete or greater than 90% control of drop attacks was achieved by 80% of patients in this extended series of patients having selective posterior callosotomy, similar to the 83% reported in the original series. This is a comparable performance to total callosotomies [7, 9, 14, 15, 20] and hence strongly suggests that preservation of the anterior callosal fibers interconnecting prefrontal regions is not relevant to surgical outcome.

Although not examined in this extended series, selective posterior callosotomy was shown to improve functionality in patients with severe encephalopathies and sudden falls [14], suggesting that in this population the occurrence or impact of a disconnection syndrome is minimal at best. Interestingly, a comprehensive metanalysis found no significant difference in the occurrence of disconnection syndrome between anterior and total callosotomies [15], highlighting the fact that section of the posterior callosal fibers may not be the crucial factor. Moreover, long-term studies following total callosotomies showed that the effects of a putative disconnection syndrome are minimal or absent in the long term [20, 32, 33].

In this extended series, younger age at surgery and shorter duration of epilepsy were predictive of favorable control of drop attacks. Patients operated before age 30 and with less than 30 years of duration of epilepsy had significantly better outcome. This is consistent with studies with other callosotomy strategies showing that surgical outcome was markedly improved when patients were operated before the end of adolescence [21], and that adults had significantly higher risk of complications [20, 33]. Because most patients in this and other series have exceedingly frequent generalised epileptic discharges and a high seizure count, early intervention likely reduces the progression of the epileptic encephalopathy. In other epilepsy scenarios, such as frontal and temporal epilepsy, younger age at surgery and shorter duration of epilepsy are also predictors of good outcome [34, 35]. In contrast age at onset of epilepsy did not correlate with outcome. Interestingly, one patient began with epileptic drop attacks at age 40 and was operated six years later, having a 97.3% reduction in seizure frequency. A comparable patient operated at the same age but after a very long duration of epilepsy had only 45% reduction in falls.

In the subgroup of 27 patients in whom this was analysed, there was no relation between surgical outcome and extent of callosal section in the posterior-to-anterior axis beyond the midbody. Tractographic evidence in 18 patients indicated that callosotomies extending to the midbody of the callosum sectioned fiber bundles interconnecting M1 and caudal SMA. Interestingly, these bundles have fibers with the largest diameter and fastest propagation [3]. Because all patients with favorable results had section of these fibers – but variable sections of more anteriorly located fiber bundles - we suggest that they have an important role in the propagation of epileptic discharges leading to drop attacks. The caudal SMA plays an important role in the execution of rapid and coordinated movements, in contrast to the rostral SMA, whose primary function is planning [36, 37]. The section of more anteriorly located fibers had no relation to outcome: two-thirds of patients free or almost free from drop attacks had residual corpus callosum fibers interconnecting the rostral SMA and other premotor areas, whereas three-fourths of those with less favorable control of atonic seizures had these more anterior fibers completely sectioned.

Probably because prefrontal callosal fibers are spared, we did not observe transient postoperative apathy, which is related to disconnection between dorsolateral and mesial portions of the anterior frontal lobe [19]. Transient or permanent hemiparesis have also been seen in patients undergoing total or anterior callosal sections, usually due to compression of the contralateral motor area or coagulation of cortical veins when reaching the interhemispheric fissure. This complication did not occur in our series as surgical access to selective posterior callosotomy is posterior to motor regions and large veins are usually absent in the surgical field [4, 38].

Although not significantly associated with outcome in the multivariate analysis, patients with structural lesions had less favorable control of epileptic falls. A glance of individual patients shows that unsatisfactory results were seen in two boys with, respectively, severe encephalitis sequelae and post-radiotherapy encephalopathy and in a woman with bilateral periventricular heterotopia. This, however, was no rule, as many patients with structural abnormalities related to perinatal ischemia and tuberous sclerosis had very good results.

EEG patterns and functionality were explored in detail in our previous publication, and we showed that pre-op EEG patterns did not impact on surgical outcome and that selective posterior callosotomy improved functionality [14]. A careful study of the electrographic changes following selective posterior callosotomy in long-term video-EEG monitoring and of object identification and reading under controlled conditions is currently being performed.

Although no direct comparative studies are available, different extensions of callosal section have been more effective in controlling drop attacks than vagus nerve stimulation [39]. The present results suggest that this favorable comparison is even more pronounced following selective posterior callosotomy, because it has lower morbidity with similar seizure outcome than total callosal sections.

Similar to our original report, this study has a number of limitations. This is a single-center cohort study that analysed a limited group of patients having epileptic drop attacks as the common denominator. Seizure quantification had to rely on diaries kept by relatives, which could lead to some inaccuracy. However, we attempted to mitigate this by focusing on atonic, tonic or massive myoclonic seizures which even when the patient was not standing led to significant head and body movements indicative of impending falls. The heterogeneity of age ranges and etiologies could be seen as precluding generalisability of the findings, although mirroring what is actually seen at busy epilepsy clinics.

In conclusion, we confirmed that selective posterior callosotomy sparing prefrontal interconnectivity is an effective and safe procedure to control drop attacks, with putative advantages over other strategies in terms of morbidity. In particular, because results are very similar to those reported with total callosotomies, selective posterior callosotomy may well be the procedure of choice in patients with these devastating epilepsies, in whom preservation of prefrontal connectivity may be a significant advantage [40].

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Figures

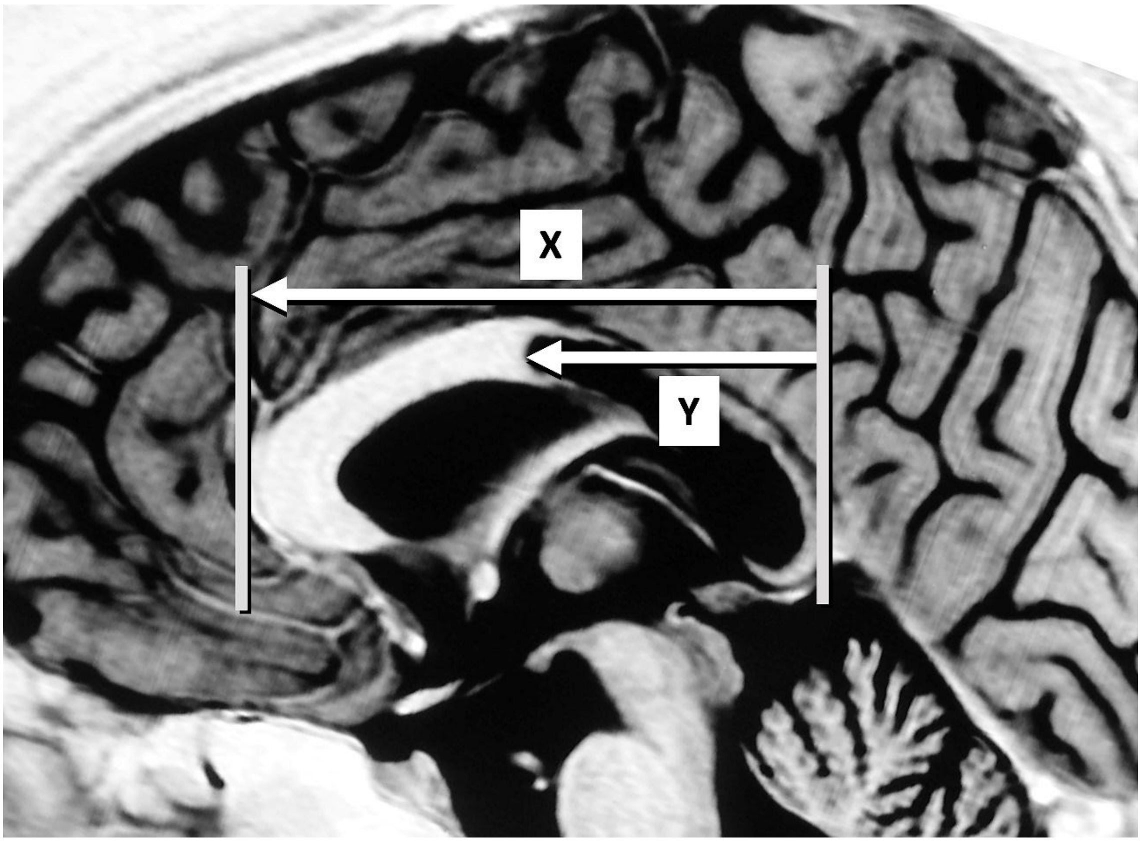

Fig. 1. Y/X: extent of posterior section of the corpus callosum as a ratio of the sectioned area (Y) and the entire callosal extension (X).

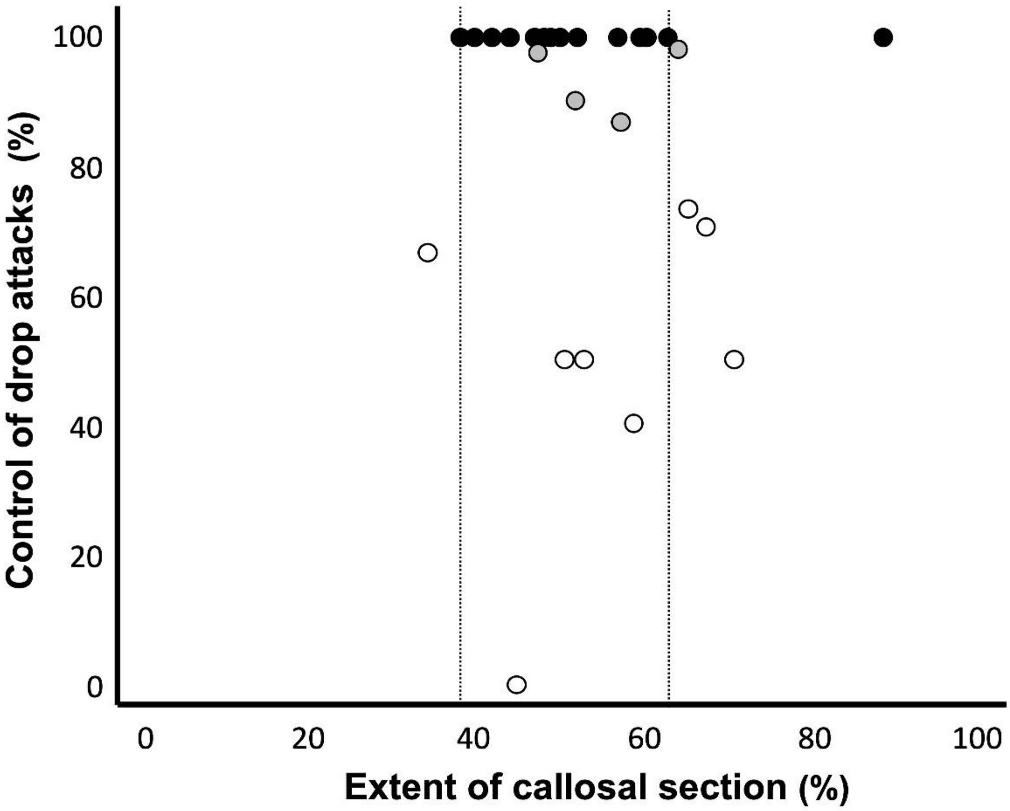

Fig 2. Lack of significant relationship between index of callosal section and rate of control of drop attacks. Note that some patients had excellent outcome and smaller sections, whereas others had extended sections but did not do as well (Table 1).

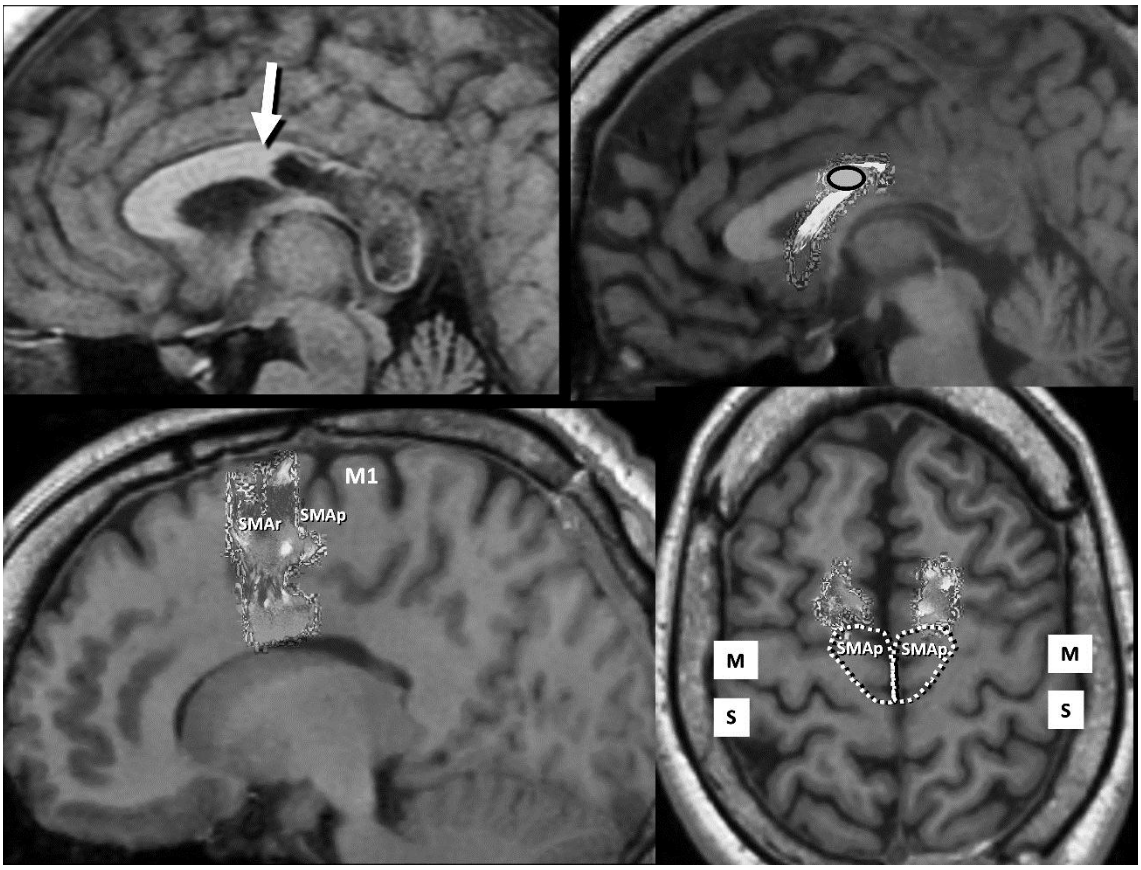

Fig 3. Post operative tractography in a patient who had selective posterior callosotomy. ROI placed at the distal remaining CC. Fibers interconnecting homologous M1 and the caudal SMA (SMA proper – SMAp) are absent while present in rostral SMA, PMA and pre frontal areas. Patient is free of drop attacks.

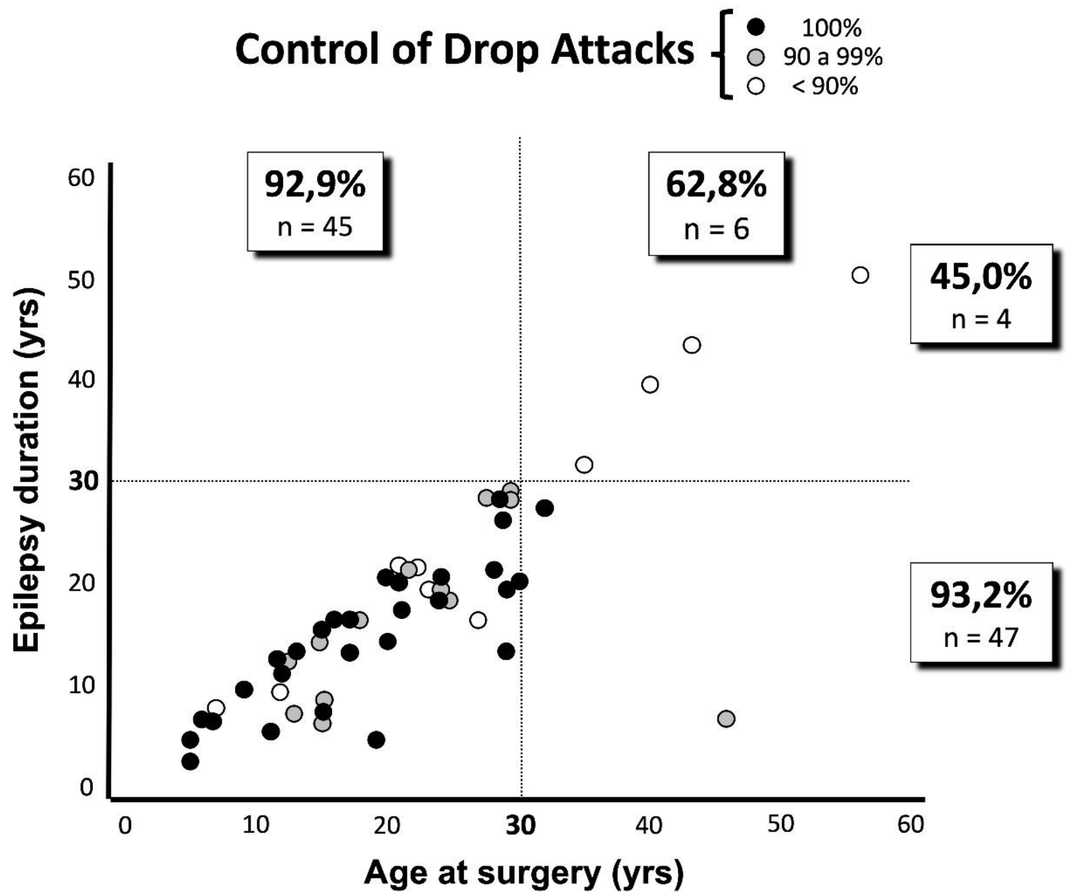

Fig 4. Graphic illustration of the multivariate relationship between age at surgery and duration of epilepsy with rate of control of drop attacks as dependent variable. Note that patients in the right upper quadrant – with longer duration and older age at operation - had the worst results.

6 CONCLUSÕES GERAIS

Os pacientes portadores de epilepsia refratária, independente da etiologia, que não apresentavam foco ressecável e com crises de atonia que foram submetidos à calosotomia posterior seletiva tiveram um ótimo resultado no controle das crises de drop attack. O procedimento é seguro, efetivo e de baixo custo (importante quando falamos em saúde pública especialmente em países em desenvolvimento). Por termos um longo seguimento podemos afirmar que o resultado do procedimento é duradouro. Nosso estudo provém suporte adicional à eficácia da calosotomia posterior seletiva e ainda define fatores prognósticos e estratégias cirúrgicas para um melhor resultado.

Através da análise de características demográficas pré operatórias e de exames de imagem pós operatórios (MRI, DTI), foi possível definirmos fatores prognósticos e a extensão posterior da ressecção necessária para um adequado controle das crises de queda. O paciente com maior probabilidade de melhora é aquele com baixa idade e baixo tempo de epilepsia. Por este motivo, combinado com a redução sustendada das crises de queda, os pacientes devem ser considerados para a cirurgia assim que houver a indicação do procedimento. Nossos achados permitem concluir que a ressecçãod as fibras da área motora primária e da área motora suplementar caudal que cruzam no istmo e porção posterior do corpo do caloso são a chave para um adequado controle das crises de queda. Fibras remanescentes conectando as áreas motora suplementar rostral e pré motora não influenciaram no outcome clínico. Pacientes com menor comprometimento cerebral parecem ter um melhor prognóstico.

Estes achados nos permitem que possamos ter uma melhor ideia de quais pacientes são excelentes candidatos ao procedimento e qual a sua perspectiva de resultado, assim como a extensão da ressecção posterior do corpo caloso necessária para um adequado controle dos drop attacks.

ANEXOS

ANEXO 1 – ARTIGO 1 - **Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity**

ARTICLES
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Selective posterior callosotomy for drop attacks

A new approach sparing prefrontal connectivity

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ABSTRACT

Objective: To evaluate a novel approach to control epileptic drop attacks through a selective posterior callosotomy, sparing all prefrontal interconnectivity.

Methods: Thirty-six patients with refractory drop attacks had selective posterior callosotomy and prospective follow-up for >4 years. Falls, episodes of aggressive behavior, and IQ were quantified. Autonomy in activities of daily living, axial tonus, and speech generated a functional score ranging from 0 to 13. Subjective effect on patient well-being and caregiver burden was also assessed.

Results: Median monthly frequency of drop attacks decreased from 150 to 0.5. Thirty patients (83%) achieved either complete or >90% control of the falls. Need for constant supervision decreased from 90% to 36% of patients. All had estimated IQ below 85. Median functional score increased from 7 to 10 ($p = 0.03$). No patient had decrease in speech fluency or hemiparesis. Caregivers rated the effect of the procedure as excellent in 40% and as having greatly improved functioning in another 50%. Clinical, EEG, imaging, and cognitive variables did not correlate with outcome.

Conclusions: This cohort study with objective outcome assessment suggests that selective posterior callosotomy is safe and effective to control drop attacks, with functional and behavioral gains in patients with intellectual disability. Results are comparable to historical series of total callosotomy and suggest that anterior callosal fibers may be spared.

Classification of evidence: This study provides Class III evidence that selective posterior callosotomy reduces falls in patients with epileptic drop attacks. *Neurology®* 2016;87:1-7

GLOSSARY

ADL = activities of daily living; **IR** = interquartile range; **SSMA** = supplementary sensorimotor area.

Epileptic drop attacks are usually refractory to medication, and their association with sudden bilateral synchronization of ictal discharges provides a rationale for callosotomy.[1,2] The procedure is indicated when focal resection is not feasible and specifically targets the sudden falls, irrespective of the underlying etiology. Thus, clinical heterogeneity of candidates is the norm.

The pioneers in sectioning the callosum for seizure control performed total callosotomies,[1] but the procedure evolved to prioritize sectioning of the anterior fibers.[3,4] However, it is the posterior extent of the callosotomy that leads to better control of drop attacks and, most importantly, when anterior or anterior two-third sections fail, extension to total callosotomy consistently improves results.[5–7]

When evaluating a patient with a small lesion in the left premotor cortex and focal thinning of the isthmus of the corpus callosum (figure 1A), our attention was drawn to the possibility that motor fibers crossed more posteriorly than previously thought. We thus modified our approach and performed section of the posterior half of the callosum in 2 patients with drop attacks and bilateral centroparietal lesions, leaving the possibility of anterior extension to total callosotomy.

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Supplemental data at Neurology.org

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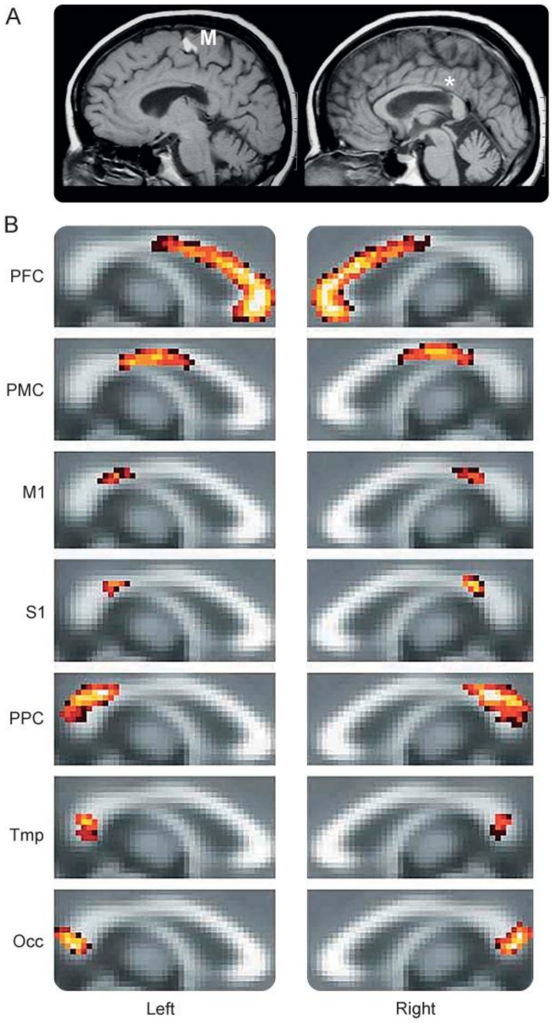
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 **Imaging evidence that fibers from the premotor cortex and primary motor cortex cross through the posterior callosum**



(A) Sagittal MRI section showing a small lesion in the border between the primary motor cortex (M) and supplementary motor area, accompanied by a focal thinning of the isthmus of the corpus callosum (asterisk). (B) Midsagittal group probability maps showing the location of cortical connections within the corpus callosum. Note that fibers from the PMC and primary motor cortex (M1) cross posterior to the midpoint of the callosum. Primary motor fibers indeed cross adjacent to the splenium. M1 = primary motor cortex; Occ = occipital; PFC = prefrontal cortex; PMC = premotor cortex; PPC = posterior parietal cortex; S1 = primary somatosensory cortex; Tmp = temporal. Panel B modified from Zarei et al.[9] with permission from the publisher, © 2006 John Wiley & Sons.

Both had sustained, complete control of the falls with posterior section only. This outcome came to be supported by anatomical[8] and imaging data[9,10] indicating that fibers from the premotor and primary motor cortex controlling axial and lower limb muscles indeed cross through the mid to posterior half of the callosum. Henceforth, we routinely offered selective posterior section to callosotomy candidates, based on the hypothesis that the improved results reported with total callosotomies were specifically related to section of the posterior fibers, rather than to the complete disconnection per se. Furthermore, because the disconnection syndrome reported with posterior callosotomy had limited effect on patients with normal cognition,[11,12] we further hypothesized that in a population with significant intellectual disability, it would be even less clinically relevant, particularly if prefrontal connectivity could be spared.[13,14]

We report a consecutive cohort of patients with disabling drop attacks and intellectual disability that underwent selective posterior callosotomy, sectioning the fibers that interconnect the motor cortices and display the fastest interhemispheric synchronization[9,10,15] (figure 1B).

METHODS This study addresses the long-term results of a novel approach to control epileptic drop attacks through selective posterior callosotomy, sparing prefrontal interconnectivity, through a cohort study providing Class III level of evidence. From April 1997 to October 2010, all patients with refractory drop attacks as the main disabling seizure type of symptomatic generalized or multifocal epilepsies underwent presurgical evaluation and selective posterior section of the corpus callosum at the Porto Alegre Epilepsy Surgery Program. The series comprises 36 patients prospectively followed for at least 4 years, with a median follow-up of 5.75 years (interquartile range [IR]: 8.9). Seven additional patients had only short follow-up. Demographic data are included in table e-1 at Neurology.org.

Interictal prolonged video-EEG recordings determined whether discharges were predominantly generalized, multifocal, or significantly lateralized. Ictal recordings were analyzed as to symmetry and discharge pattern: polyspikes, polyspike slow waves, or diffuse attenuation following generalized spike-slow waves. MRI was performed in a 1.5T Siemens scanner (Siemens AG, Erlangen, Germany). Neuropsychological evaluation estimated IQ through subtests of the Wechsler Adult Intelligence Scale–Revised or Wechsler Intelligence Scale for Children. Patients were considered able to read simple sentences if they could read out loud "It is a beautiful day." All were stabilized on a combination of valproate, lamotrigine, and a benzodiazepine for at least 6 months before surgical decision[16] and were kept in this regimen after operation. Doses were allowed to change over the years, according to occasional relapses or side effects.

Pre- and postoperative epileptologic and functional evaluation. Relatives were interviewed to assess demographic and etiologic data, level of dependence in activities of daily living (ADL), need for constant supervision, and episodes of aggressive behavior. During the 3-month baseline period and following surgery, relatives were instructed to keep seizure diaries, taking note of drop attacks. They were not instructed to register other seizure types. Frequency of falls was analyzed in absolute numbers and also categorized as follows: at least daily, weekly, monthly, yearly, or less frequently than once a year.

Neurologic examination and parental reporting classified patients as dependent or independent for ADL, including praxis to feed, dress, and button (text e-1), and whether constant supervision was needed. Episodes of aggressiveness were categorized as occurring rarely, monthly, weekly, or daily. Ability to sustain the head and stand was rated as normal or abnormal. Gait could be independent or needing assistance and word articulation could be fluent, comprehensible, or incomprehensible. From these neurologic and functional data, we generated a composite functional score ranging from 0 to 13 points (text e-1).

Following operation, relatives were asked to register drop attacks and episodes of behavioral dyscontrol. They were also asked to rate the effect of the procedure as excellent, improved, unchanged, or worsened according to well-being of the patients and burden of the caregivers. Seizure, behavioral, and functional data were obtained prospectively after surgery, through outpatient visits every 6 to 12 months and telephone contact with the clinic between consultations. Most recent functional and behavioral data were assessed through a structured questionnaire by trained interviewers blinded to preoperative data.

Surgical procedure, postoperative antiepileptic drug management, and evaluation of outcome. Surgical technique is illustrated in figure e-1 and described in text e-2. Because section should include fibers originating from the premotor, supplementary sensorimotor area (SSMA), and primary motor cortex,[9] including those associated with ictal negative motor phenomena,[17,18] 50% to 60% of the callosum needed to be disconnected in the posterior-to-anterior axis, as judged by postoperative MRI (figure 2). Fibers interconnecting the frontal lobes anterior to the SSMA were spared.

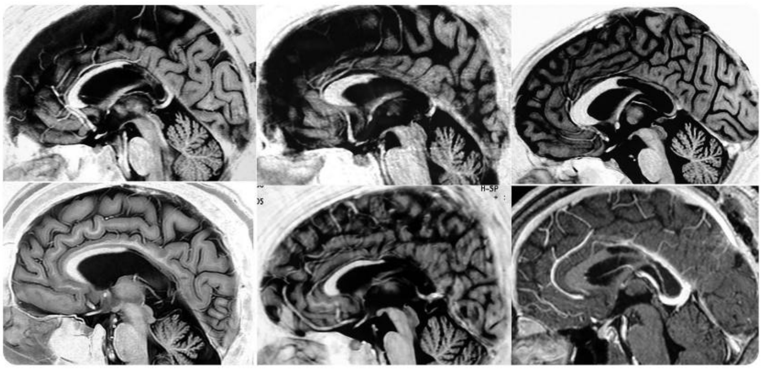
Standard protocol approvals, registrations, and patient consents. The study was performed in the setting of managing patients with very severe epilepsies. The procedure was explained in detail to relatives, including why selective posterior callosotomy was being offered, the expected seizure and functional outcomes, and a critical appraisal of the possible complications. All gave written informed consent to the procedure and to the publication of data. The study was approved by the institutional ethics committee.

Statistics. SPSS Statistics version 19 (IBM Corp., Armonk, NY) was used. Wilcoxon signed rank test for ordinal and continuous variables and the McNemar test for dichotomous variables were used. In addition, Poisson regression was applied for multivariate analyses.

RESULTS Twenty-four patients were male and 29 were right-handed. Mean age at epilepsy onset was 2.8 years (SD 3.5) and that of drop attacks 6.4 years (SD 4.6). Mean duration of epilepsy before operation was 18.1 years (SD 11.6) and age at surgery 21.5 years (SD 11.3).

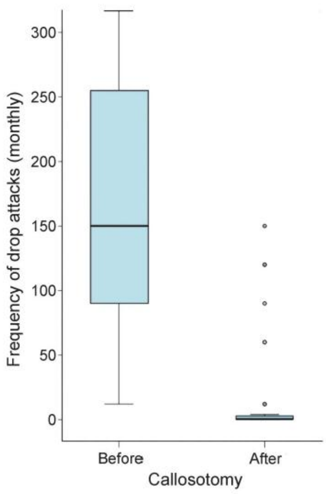
Control of drop attacks. Median preoperative frequency of drop attacks per month was 150 (IR: 187.5) and reduced to 0.5 (IR: 3.5) after posterior callosotomy (figures 3 and 4). Seventeen patients (47%) achieved complete control of the falls, often following a running down course over the first 3 months. In this subgroup, preoperative median monthly frequency of drop attacks was 180 (IR: 220). The other 19 patients who still had drop attacks following posterior callosotomy had a median of 150 falls (IR: 120) preoperatively and a median of 2 falls after operation (IR: 59.5). Thirteen of the latter 19 (68%) had a >90% reduction in the frequency of falls. Thus, 30 of 36 patients (83%) had complete or >90% control of drop attacks and only 6 patients (17%) were not significantly improved

Figure 2 Composite picture of postoperative MRIs in the midsagittal plane of 6 patients undergoing selective posterior callosotomy



The section on the right, bottom row, is a contrasted T1 image. All others are inversion recovery images.

Figure 3 **Boxplot of median and interquartile range of pre- and postoperative frequency of drop attacks**



Circles in the postoperative column represent individual patients. Note that all others are clustered within a median of 0.5.

by the procedure (figure 4). Preoperatively, 32 patients (89%) had daily falls and the other 4 fell at least once a week. Following selective posterior callosotomy, only 6 patients (17%) fell daily and 3 (8%) at least once a week ($p = 0.0001$) (figure e-2A). Need for constant supervision declined from 90% to 36% of patients after surgery. Five patients (14%) had a clinical and EEG picture compatible with the Lennox-Gastaut syndrome. Preoperative frequency of drop attacks did not differ in these patients compared to the other 31 ($p = 0.19$; text e-3), and surgical results were similar. Control of drop attacks according to MRI findings is shown in table e-2.

Neurologic, behavioral, and functional effect. Table e-3 lists pre- and postoperative autonomy in ADL. No patient had significant dyspraxia or worsened in any ADL or in the ability to sustain the head and stand. Median functional score increased from 7 to 10 postoperatively ($p = 0.03$) (figure e-3A). No patient had akinetic mutism, decrease in speech fluency, hemiparesis, or other complications that could be attributed to the procedure. Nine patients (25%) were able to read simple sentences before operation and continued to read afterward.

Preoperatively, bouts of aggressive behavior occurred at least once a week in 16 patients (44%) but in only 5 (14%) after operation. Overall, 15 (43%) had significant reduction in aggression and only 4 (11%) worsened. Caregivers rated the procedure as having had an excellent result in 40% of patients and having greatly improved functionality in another 50%. Only one patient was judged as worsened (figure e-3B). Four patients had venous air embolism detected with Doppler, and correction measures were performed without postoperative clinical consequences. All patients were ambulatory on the second postoperative day.

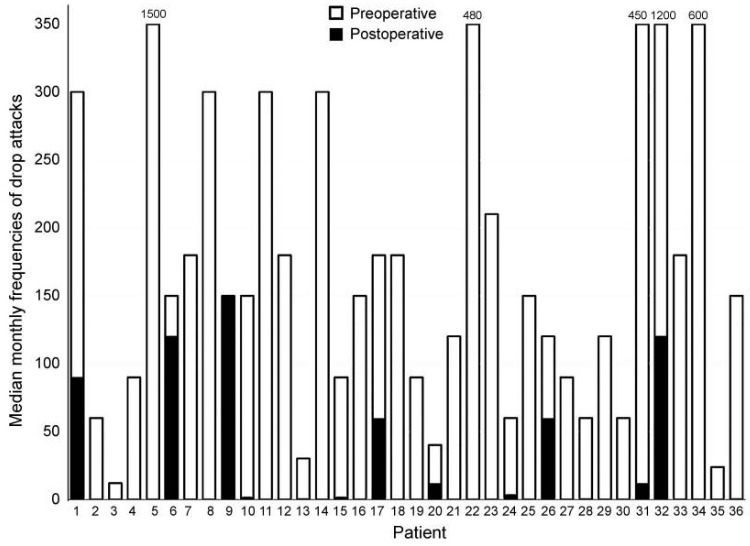
Electrographic, imaging, and cognitive findings. These findings are summarized in table e-4 and detailed in text e-3. There was no significant relationship between cognitive, electrographic, or imaging abnormalities and degree of control of drop attacks. Postoperatively, 10 of the 23 patients (43%) with predominantly generalized EEG discharges changed to a predominantly lateralized pattern. The other 13 patients, with predominantly multifocal or distinctly lateralized discharges in the preoperative EEG, did not have notable EEG changes.

Multivariate analysis. Included in the multivariate analysis were those variables with a $p < 0.20$ in the bivariate analysis: imaging findings, age at seizure onset, epilepsy duration, and variability of the composite functional score. Only the latter remained significantly correlated with seizure outcome (relative risk = 1.25; 95% confidence interval: 1.02–1.54; $p = 0.034$) (figure e-2B).

DISCUSSION Traditionally, callosotomy targets the anterior third, half, or two-thirds of the corpus callosum, thus primarily disconnecting the frontal lobes.[2–5] However, variable extensions of anterior callosotomy frequently fail to control drop attacks and results consistently improve following additional posterior section.[5–7] This raises the possibility that fibers crossing through the posterior callosum may be specifically relevant to epileptic falls, as suggested by anatomical, imaging, and neurophysiologic data.[8,9,15] In our consecutive cohort of patients undergoing selective posterior callosotomy, results compared favorably with historical series of total callosotomy,[7,19,20] suggesting that disconnecting the prefrontal regions may not be necessary for control of drop attacks. The favorable results with posterior sections in our initial patients led us to systematically propose this procedure. Because the results challenge long-held views on surgical strategy and cognitive risks, we included only patients with 4 or more years of follow-up.

Our study has a number of limitations. First, pre- and postsurgical frequencies of drop attacks were not documented through video-EEG monitoring. Seizure diaries may underestimate these, because atonic, tonic, or myoclonic attacks potentially leading to falls may occur when patients are not standing. However, although a placebo effect could occur in the early

Figure 4 Median monthly frequencies of drop attacks before and after selective posterior callosotomy in each of the 36 patients



Frequencies above 350 are specifically indicated.

postoperative period, it is unlikely that it would persist for many years after the procedure. Second, this is a cohort study analyzing seizure outcome in an uncontrolled fashion. We tried to enhance the reliability of the findings by following patients closely, restricting the analysis only to drop attacks—the seizure type most unlikely to be missed by caregivers—and having final outcome data collected by interviewers blinded to preoperative findings. As in most series, preoperative frequency of drop attacks was high, and it would probably be artificial to compare results following surgery with a "control" group of patients on a waiting list, as has been the case with temporal lobectomy.[21] Third, we devised a pragmatic functional score based on simple ADL representing the difficulties faced by patients and caregivers. Although it has not been validated, it addressed the major question regarding a posterior disconnection, namely, whether it would compromise functional integration at a level that would negatively interfere with the daily lives of patients with intellectual disability. The fact that functional scores increased after surgery suggests that, in this population, selective posterior callosotomy is functionally safe.

Callosotomy is offered to patients with diffuse brain dysfunction who cannot have a focal resection and usually involves the anterior third,[3,4] anterior half,[19] anterior two-thirds,[4,7] everything but the splenium[22] or the totality of the callosum.[5,7,23] The idea to shift the paradigm toward selective posterior callosotomy was supported by the consistent improvement of control of generalized seizures when anterior sections are extended to complete sections.[19] A recent report from the Mayo Clinic showed complete control of drop attacks in 13 of 22 patients (60%) who had 1- or 2-stage complete callosotomy but in only 8 of 33 (24%) in whom only the anterior two-thirds of the callosum was sectioned.[7] Of note, 5 of the latter had extension into complete section and 4 (80%) became free of drop attacks. In the study reporting the best results, 1-stage total callosotomy completely controlled drop attacks in 25 of 34 patients and led to a >90% improvement in 6 others.[20]

Compared to data pooled from a systematic review[24] including studies reporting specifically on control of drop attacks with variable extents of anterior and total callosotomy in children,[6,25–28] our patients were twice as old and epilepsy duration and postoperative follow-up were twice as long (table e-1). Although our series was not restricted to pediatric patients, it is interesting to note that the rate of at least >90% reduction in the frequency of drop attacks was almost exactly the same in our patients undergoing *selective posterior callosotomy* and in the patients undergoing *total callosotomy* pooled from this review (83.3% vs 83.5%). Moreover, the selective posterior approach appears more efficacious than different extensions of anterior sections in adults.[22,23] In the updated Montreal Neurological Institute series of anterior callosotomy, only 38% of patients were completely free of falls and 34% had a >75% response.[4]

The fact that results with posterior section are comparable to those of historical series of complete disconnections (and particularly to *completed* callosotomies following unsuccessful anterior sections) suggests that fibers crossing in the posterior half of the callosum are key to drop attacks. It also suggests that it is not interhemispheric synchronization of epileptic discharges per se, but rather the synchronization of the fibers originating in the motor and premotor cortex, including the negative motor cortex,[17] that are relevant to the mechanism of falls. This is supported by the lack of correlation between the persistence of bisynchronous discharges on postoperative EEG and control of drop attacks in our and other studies.[20]

There are few reports of patients undergoing selective posterior callosotomy to control drop attacks and the rationale was not stated.[13,19] However, anatomical and histologic data do suggest a solid rationale for the posterior section,[9,15] and tractography studies confirm that fibers originating in the premotor, SSMA, and primary motor cortex cross around and posterior to the isthmus of the corpus callosum up to the borders of the splenium.[9] Furthermore, the majority of large fibers (>5 μm) cross posteriorly in the corpus callosum, whereas 70% of the fibers in the genu are 10 times thinner.[15] Therefore, resections of the anterior third, half, and two-thirds of the callosum miss most fast conducting fibers, the subsequent section of which in 2-stage total callosotomies predictably improves outcome.

The interhemispheric traffic of visual, tactile, and auditory information is fundamental to integrate environmental stimuli with specialized posterior association cortices supporting language, gnosis, and praxis.[11,29–31] Based on an extensive literature, we assumed there was a disconnection syndrome when sectioning the posterior callosum. However, recent accounts of the long-term functional follow-up of patients undergoing total callosotomies describe how little effect such disconnections may have outside the laboratory setting.[12,32] Thus, we opted for an assessment of the effect of such disconnection in ADL and showed that this is of minor significance in patients with intellectual disabilities, as suggested by improved postoperative scores in our straightforward functionality index. There was also a correlation between continued freedom from drop attacks and functional score, suggesting that control of falls is important for gains in functionality. These results suggest that in patients with generalized or multifocal epilepsies, uncontrolled drop attacks and intellectual disability, a pragmatic view of the posterior disconnection syndrome may be appropriate and should not preclude the option for selective posterior callosal section.

Although usually transient, akinetic mutism, ataxia, and poor sphincter control can follow anterior callosotomy and increase morbidity in the postoperative period.[33] Such abnormalities were not seen in our patients. Although we did not directly compare patients with total vs selective posterior callosotomy, data on the role of prefrontal connectivity, particularly the integration between stimulus-related semantic and episodic information,[13] suggest that patients may benefit from sparing prefrontal fibers, providing control of drop attacks is similar. Furthermore, the favorable functional outcome reported by the caregivers is in line with the view by Gazzaniga et al.[34] that whatever commissural fibers remain intact may be sufficient for interhemispheric transfer of information, supporting the sparing approach. Finally, the most common surgical complications of callosotomies, including hemiparesis, language disturbances, and ataxia, are often related to manipulation of the pericallosal arteries and cingulate gyrus, which is obviated by selective posterior callosotomy.

In a systematic review, variable extensions of callosotomies led to higher control of drop attacks than vagus nerve stimulation.[35] Our results further suggest that selective posterior callosotomy is likely to be even more efficacious and safe than the combined results of different extensions of callosal section, thus providing potential additional advantage over vagus nerve stimulation.

Finally, despite the overall good results, selective posterior callosotomy was still ineffective in approximately 20% of patients, suggesting heterogeneous epileptogenic mechanisms leading to falls. Future studies with larger patient samples may be powered to detect specific subgroups with more or less favorable prognoses.

AUTHOR CONTRIBUTIONS

Design, data collection, management, analysis and interpretation of the data, as well as preparation, review, and approval of the manuscript were under the control and responsibility of the authors. E.P. and A.P. designed the study, coordinated data collection, and wrote the first draft of the manuscript. M.P. obtained and interpreted all neuropsychological data, and wrote parts of the manuscript. J.R.H. and R.S. obtained and interpreted imaging data, and wrote parts of the manuscript. T.F., L.P., R.S. collected all data. W.M. organized the data bank and the statistics. N.A., J.C.C., M.H., and T.T. critically reviewed the manuscript and directly influenced the final format of the submission.

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DISCLOSURE

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Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity

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DISCUSSÃO – ARTIGO 1

O artigo intitulado “Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity” é um trabalho original publicado na Neurology em 2016 que teve como objetivo descrever a avaliar os resultados no controle de crises de atonia em pacientes submetidos ao procedimento.

Esta foi a primeira série publicada pelo grupo do Programa de Cirurgia de Epilepsia do Hospital São Lucas da PUCRS sobre a técnica desenvolvida pelo Dr. Eliseu Paglioli Neto em 1997. Esta cohorte prospectiva de nível III de evidência, comprovou a eficácia e segurança desta nova técnica. Os resultados no controle das crises de atonia foram muitos superiores aos obtidos coa calosotomia anterior e similares aos obtidos com a calosotomia total, porém com menor morbidade. Pacientes desta série não apresentaram apatia e sindrome de desconexão severas relatadas em outras séries de calosotomia total. Além do controle das crises, o procedimento proporcionou aos pacientes ganhos cognitivos e nos níveis de independência o que sugere que as fibras pré frontais podem ser poupadas sem prejuízo no *outcome*.

ANEXO 2 – ARTIGO 2 – **Microsurgical anatomy of the central lobe**

JNS

LABORATORY INVESTIGATION
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Microsurgical anatomy of the central lobe

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OBJECT The central lobe consists of the pre- and postcentral gyri on the lateral surface and the paracentral lobule on the medial surface and corresponds to the sensorimotor cortex. The objective of the present study was to define the neural features, craniometric relationships, arterial supply, and venous drainage of the central lobe.

METHODS Cadaveric hemispheres dissected using microsurgical techniques provided the material for this study.

RESULTS The coronal suture is closer to the precentral gyrus and central sulcus at its lower rather than at its upper end, but they are closest at a point near where the superior temporal line crosses the coronal suture. The arterial supply of the lower two-thirds of the lateral surface of the central lobe was from the central, precentral, and anterior parietal branches that arose predominantly from the superior trunk of the middle cerebral artery. The medial surface and the superior third of the lateral surface were supplied by the posterior interior frontal, paracentral, and superior parietal branches of the pericallosal and callosomarginal arteries. The venous drainage of the superior two-thirds of the lateral surface and the central lobe on the medial surface was predominantly through the superior sagittal sinus, and the inferior third of the lateral surface was predominantly through the superficial sylvian veins to the sphenoparietal sinus or the vein of Labbé to the transverse sinus.

CONCLUSIONS The pre- and postcentral gyri and paracentral lobule have a morphological and functional anatomy that differentiates them from the remainder of their respective lobes and are considered by many as a single lobe. An understanding of the anatomical relationships of the central lobe can be useful in preoperative planning and in establishing reliable intraoperative landmarks.

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KEY WORDS central lobe; cerebral arteries; cerebral veins; craniometrics; gyrus; microsurgical anatomy; sulcus

THE central lobe, composed of the pre- and postcentral gyri and the paracentral lobule is one of the most eloquent areas of the brain, and it corresponds to the sensorimotor cortex. This morphological unit, together with the functional interaction between motricity and sensitivity, justifies the characterization of these gyri as a single lobe.[45]

There have been several studies of gyral and sulcal anatomy, craniometrics, and vascular features that included this area.[1,4,10,11,17,19,21–24,28,36,39–41,43–46,51,54,56,57] However, important details are still lacking. The aim of the present study is to define the neural features, craniometric relationships, arterial supply, and venous drainage of the central lobe.

Methods

The central lobe was examined under magnifications of ×3 to ×40 in 20 formalin-fixed cadaveric hemispheres in which the arteries were perfused with red and the veins with blue silicone. The frontal and parietal bones were removed while preserving the coronal suture to study its relationship with the anterior and posterior limits of the precentral gyrus. The arachnoid membrane was removed from the gyral surfaces and variations in the sulci and gyri were examined. The inclination of the central sulcus and coronal suture compared with their coronal planes was measured. The distances between the coronal suture and the anterior and posterior limits of the precentral gyrus

ABBREVIATIONS ACA = anterior cerebral artery; AVM = arteriovenous malformation; MCA = middle cerebral artery.

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were established at 1 cm intervals from their upper to their lower ends. The arterial branches supplying the central lobe were followed from their origin to their termination. The sylvian fissure was opened widely to determine the arterial trunks, stem arteries, and cortical branches supplying the central lobe. The veins and drainage pathways of the central lobe were defined.

Results

Topographical Anatomy

The lateral surface of the central lobe includes the precentral and postcentral gyri divided by a central sulcus and limited anteriorly by the precentral and posteriorly by the postcentral sulcus (Fig. 1). It folds over the superior border of the hemisphere to include the paracentral lobule, limited by the paracentral sulcus anteriorly, the ascending ramus of the cingulate sulcus posteriorly, and the cingulate sulcus below (Fig. 1C and D). The ascending ramus was present in all examined hemispheres and is easily seen on the MRI's sagittal cuts. Therefore it is a useful landmark in determining the position of the paracentral lobule. The paracentral sulcus was found in 50% of the examined hemispheres.

The central sulcus is one of the most constant sulci on the cerebral surface. It is not usually interrupted above its lower end where a gyral bridge between the pre- and postcentral gyri called the subcentral gyrus (Broca's inferior frontoparietal pli de passage) separates the central sulcus from the sylvian fissure (Fig. 1; Table 1).[9] The upper end opened directly into the interhemispheric fissure in most hemispheres.[19,46] The central sulcus was located an average of 5.3 cm (range 4.7–5.9 cm) behind the coronal suture at its upper end and 3.8 cm (range 2.8–4.4 cm) at its lower end.

From its upper end, the central sulcus has a posterior-to-anterior and medial-to-lateral trajectory forming an angle of approximately 20° with the coronal plane passing through its upper end. It has 2 sinusoidal curves, or genua. Its upper half is gently convex posteriorly and its lower half is gently convex anteriorly (Figs. 1 and 2).[40]

The precentral gyrus has the same orientation and trajectory as the central sulcus and presents the same curvatures. The upper genu corresponds to the motor area of the hand (Fig. 1E).[9,58] The anterior edge of the precentral gyrus was located an average of 3.6 cm (range 3.0–4.3 cm) behind the coronal suture at its upper end and 2.3 cm (range 1.3–3.2 cm) at its lower end, but at the closest point, at approximately the level where the superior temporal line crosses the coronal suture, they were separated by an average of 1.8 cm (range 0.6–3.3 cm; Table 2).

The lower third of the central sulcus has a relatively constant relationship with the central sulcus of the insula in that it coursed superficial and almost parallel to the central sulcus of the insula in 7 of 20 examined hemispheres (Fig. 1F). Of the remaining hemispheres, the lower end of the central sulcus was located an average of 0.2 mm anterior to the central insular sulcus in 7 cases and 0.41 mm posterior in 6 cases.

The precentral gyrus is positioned lateral to the following structures: the body of the lateral ventricle, the thalamus, the posterior limb of the internal capsule, the posterior part of the lentiform nucleus, and the midportion of the insula.[40] The precentral sulcus is positioned posterior to the pars opercularis of the inferior frontal gyrus, which provides a good anatomical reference for identifying the lower part of the precentral sulcus. At its upper end the precentral sulcus opened directly into the interhemispheric fissure in 9 of the 20 hemispheres and at its lower end directly into the sylvian fissure in 13. The precentral sulcus was interrupted by 1–3 gyral bridges in all hemispheres (Table 1). These gyral bridges could connect the precentral gyrus to the superior, middle, or inferior frontal gyrus. The postcentral gyrus corresponds to the somatosensory area of the cerebrum. It is narrower than the precentral gyrus, a characteristic useful to differentiate the gyri in the surgical field. It also follows the curvatures of the central sulcus, and is typically segmented by gyral bridges. The postcentral sulcus opens directly into the interhemispheric fissure and/or the sylvian fissure in about half of the hemispheres (Table 1). The postcentral gyrus has a constant relationship with the intraparietal sulcus, typically coursing perpendicular to it. The intraparietal sulcus joined the postcentral sulcus in most hemispheres and is a useful anatomical landmark for surgical guidance and also a corridor to approach some atrial lesions.[42] It divides the parietal lobe into the superior and inferior parietal lobules. The postcentral gyrus is usually crossed by 1 or 2 gyral bridges connecting it to the superior parietal lobule and/or the supramarginal gyrus (Table 1). The inferior edge of the postcentral gyrus consistently faces the anterior transverse temporal (Heschl's) gyrus across the sylvian fissure.[57]

Craniometric Relationships of the Coronal Suture

The coronal suture extends from the bregma (union between the sagittal and coronal sutures) above to its lower end at the pterion (area of convergence of frontal, temporal, sphenoid, and parietal bones; Fig. 2A, B, and D). It is easily palpable through the scalp and, therefore, is a helpful and reliable anatomical landmark. From its upper end, it has a descending trajectory from medial to lateral and posterior to anterior. Its upper portion runs almost perpendicular to the midline but near where it crosses the superior temporal line its forward inclination increases. It crosses the superior and inferior frontal sulci and has a trajectory somewhat parallel to the central lobe. It is longer than the precentral gyrus and the central sulcus. It had an average length of 10.5 cm (range 10.0–11.2 cm), while the length of the precentral gyrus and central sulcus averaged 10.1 cm (range 9.6–10.6 cm) and 9.5 cm (range 8.6–10.0 cm), respectively.

As the coronal suture and the precentral gyrus descend from their upper ends, they converge, becoming closer together. A useful landmark, the point where the superior temporal line crosses the coronal suture, was located an average of 7.6 cm (range 7.1–8.6 cm) lateral to the midline along the coronal suture and was usually at or near the level of maximal proximity (Fig. 2A and B). The closest point between the suture and the precentral gyrus was located approximately 6 cm lateral to the bregma along the coronal suture in 50% of the specimens and 7 or 8 cm

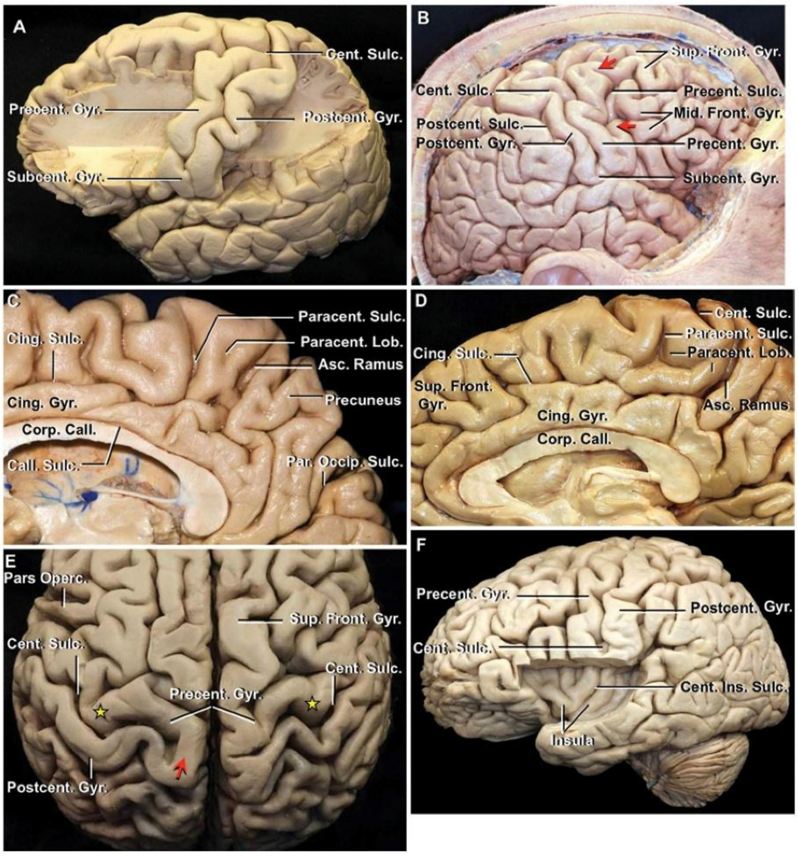

FIG. 1. Gyral and sulcal variations in multiple hemispheres. **A:** Part of the frontal and parietal lobes has been removed while preserving the pre- and postcentral gyri separated by a central sulcus. The central sulcus commonly opens directly into the interhemispheric fissure but is separated from the sylvian fissure by a gyral bridge, the subcentral gyrus. It has a gently convex posterior upper curve and a gently convex anterior lower curve. The shallow indention on the subcentral gyrus is not a sulcus but is related to an artery crossing the gyrus. **B:** Gyral bridges frequently interrupt the precentral and postcentral gyri but not the central sulcus (Table 1). The postcentral sulcus in this hemisphere is continuous and not interrupted by any gyral or sulcal bridge. The central sulcus opens into the interhemispheric fissure but is separated from the sylvian fissure by a subcentral gyrus. Two complex gyral bridges *(red arrows)* connect the superior and middle frontal gyri to the lower part of the precentral gyrus. **C and D:** Medial surface of two right hemispheres. **C:** The paracentral lobule is formed by the extension of the pre- and postcentral gyri onto the medial surface of the hemisphere. The paracentral lobule is limited posteriorly by the ascending ramus of the cingulate sulcus and anteriorly by the paracentral ramus of the cingulate sulcus. The paracentral sulcus was present in approximately half of hemispheres. The ascending ramus was found in nearly all hemispheres and is easily seen on MRI at the posterior edge of the paracentral lobule. The precuneus is located between the ascending ramus and the parietooccipital sulcus. **D:** The paracentral sulcus, which was absent in approximately 50% of hemispheres, does not reach the upper margin of this hemisphere. The anterior limit of the paracentral lobule can be determined by the overlap of the central sulcus onto the medial surface. **E:** Superior view. On the left hemisphere there is a large gyral bridge *(red arrow)* connecting the upper edges of the pre- and postcentral gyri and separating the upper end of the central sulcus from the interhemispheric fissure. The "hand knob" on the precentral gyrus is seen in both hemispheres *(yellow stars)*. **F:** Lateral surface. The lower third of the central sulcus usually courses lateral and parallel to the central insular sulcus. Asc. = ascending; Cent. = central; Cing. = cingulate; Corp. Call. = corpus callosum; Front. = frontal; Gyr. = gyrus; Ins. = insular; Lob. = lobule; Mid. = middle; Occip. = occipital; Operc. = opercularis; Par. = parietal; Paracent. = paracentral; Postcent. = postcentral; Precent. = precentral; Subcent. = subcentral; Sulc. = sulcus; Sup. = superior.

TABLE 1. Sulcal continuity and interruption by gyral bridges

Sulci	No. of Hemispheres (%) Continuity	Discontinuity	Observation
Central sulcus	19 (95)	1 (5)	Opened directly into the interhemispheric fissure in 80%; subcentral gyrus found in 85%
Precentral sulcus	0 (0)	1 bridge in 9 (45), 2 bridges in 7 (35), 3 bridges in 4 (20)	Opened directly into the interhemispheric fissure in 45% & into the sylvian fissure in 65%
Postcentral sulcus	1 (5)	1 bridge in 10 (50), 2 bridges in 9 (45)	Opened directly into the interhemispheric fissure in 45% & into the sylvian fissure in 60%; gyral bridges w/ superior parietal lobule in 70% & supramarginal gyrus in 65%

in each of the other 25%, respectively. After reaching the point of maximal convergence, the suture and the gyrus diverge toward their lower ends, where they are still closer than at their upper ends (Table 2). The anterior inclination of the central sulcus is greater in its upper half than in its lower half. The opposite happens with the coronal suture. Its inclination is lower in its upper half and greater at its lower end (Fig. 2E and F; Table 3).

Arterial Supply

The middle cerebral artery (MCA) and the anterior cerebral artery (ACA) supply the central lobe (Figs. 3 and 4).[44] The pericallosal artery is the portion of the ACA distal to the anterior communicating artery that runs adjacent to the corpus callosum. It provides most of the cortical branches that supply the medial surface and the upper part of the lateral surface of the cerebrum, including the paracentral lobule and the upper portion of the central lobe, bordering the interhemispheric fissure. The callosomarginal artery is the largest branch of the ACA and is defined as the branch running in or above the cingulate sulcus that gives rise to 2 or more cortical branches. Its branches may also supply the paracentral lobule as well as the upper portion of the central lobe on the lateral surface.

The ACA cortical branches that contribute to the arterial supply of the central lobe were the posterior internal frontal, paracentral, and superior parietal arteries (Fig. 3). The posterior internal frontal artery coursed along and supplied some of the medial surface of the frontal lobe. It had an upward and backward trajectory folding around the superior margin to reach the lateral surface, and supplied the anterosuperior part of the precentral gyrus in 18 hemispheres. It did not provide any supply to either the paracentral lobule or the postcentral gyrus. The posterior internal frontal artery arose from the callosomarginal artery in 7 hemispheres and the pericallosal artery in 13. In 8 hemispheres it supplied the full width of the precentral gyrus and in 10 the anterior half only. The lowest point reached on the lateral surface by the posterior internal frontal artery was 3 cm lateral to the superior edge of the precentral gyrus (Fig. 3).

The paracentral artery arose from the pericallosal artery in 15 hemispheres and the callosomarginal artery in 5, and it commonly coursed on the cingulate sulcus between the paracentral sulcus and the ascending ramus of the cingulate sulcus. Above the cingulate sulcus, before reaching the ascending ramus, it turned up toward the superior border and gave branches that supplied the paracentral lobule and the upper portion of the pre- and postcentral gyri on the lateral surface. It supplied the anterior part of the paracentral lobe in all hemispheres and the posterior portion in 17 of 20 hemispheres. After folding over the superior margin of the hemisphere, it supplied the upper portion of the precentral gyrus in 14 hemispheres and the upper portion of the postcentral gyrus in 16 hemispheres. On the lateral surface it reached as low as 1.6 cm from the superior border.

The superior parietal branch of the pericallosal artery arose anterior to the splenium of the corpus callosum and coursed in or close to the ascending ramus of the cingulate sulcus. It supplied the anterior portion of the paracentral lobule in 5 hemispheres and the posterior portion in 17 hemispheres. On the lateral surface, it irrigated the upper part of the postcentral gyrus in 8 hemispheres. It did not supply the precentral gyrus. The most common area supplied by the superior parietal artery in the central lobe was the posterior portion of the paracentral lobule.

The MCA supplies the entire central lobe on the lateral surface, except the upper part bordering the superior margin of the hemisphere supplied by the cortical branches of the ACA (Figs. 4 and 5).[44] The MCA bifurcated into superior and inferior trunks in 16 hemispheres and trifurcated into anterior, middle, and superior trunks in 4 hemispheres. The central lobe was supplied by the central, precentral, and anterior parietal branches of the MCA.

The central artery supplied a larger part of the central lobe than any other artery (Figs. 4–6). It arose from a stem artery (the arterial segment between a postbifurcation trunk and a cortical branch) as double or triple branches. In this study the central artery was found to be a double artery in 80% of the specimens and a triple artery in 20%. It supplied part of the precentral and postcentral gyri in all hemispheres. The most frequent pattern found (14 hemispheres) was for the central artery to arise from a stem artery arising from the superior trunk at or slightly before the stem artery exited the sylvian fissure (Figs. 5 and 6). In the MCAs with a trifurcation, the stem artery that gave origin to the central arteries arose from the middle trunk. In 2 hemispheres a small central artery arose from the inferior trunk.

The precentral artery irrigated the anterior portion of the precentral gyrus in 14 hemispheres. It arose from a superior trunk in 18 hemispheres, from a middle trunk of an MCA trifurcation in 1, and from an early frontal branch in 1. It did not reach the postcentral gyrus in any hemisphere.

The anterior parietal artery irrigated the posterosuperior portion of the postcentral gyrus in 16 hemispheres. It arose from the superior trunk in 14 hemispheres and from the inferior trunk in 2 hemispheres. In 6 hemispheres it

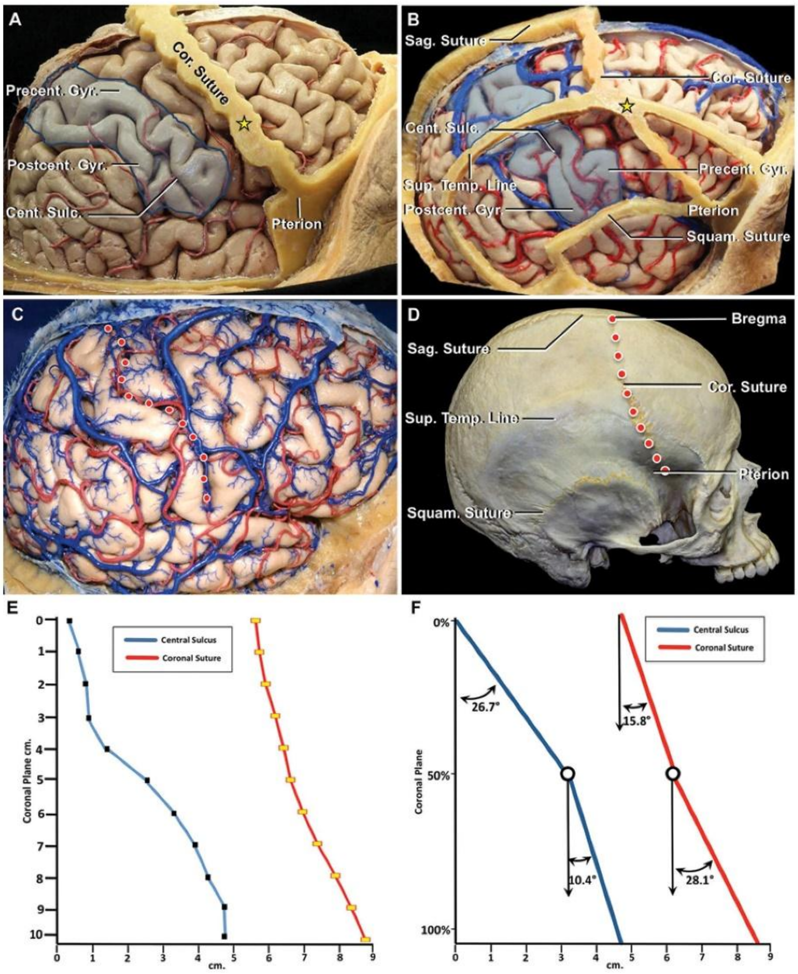

FIG. 2. A: The right coronal suture and the precentral gyrus converge as they descend from their upper ends and become closer. The point of maximal convergence is approximately at the junction of the superior temporal line and the coronal suture (*yellow star*). This point, named the stephanion, is located an average of 7.6 cm lateral to the midline along the coronal suture. **B:** The anterior edge of the right precentral sulcus is closest to the coronal suture around 1 cm lateral to the point where the superior temporal line crosses the coronal suture *(yellow star)* as was found in 25% of the hemispheres. Below this point they diverge, but their lower ends remain closer than their upper ends. **C and D:** Typical course of the central sulcus (C) and coronal suture (D) (*red dots* measured at 1-cm intervals) starting superiorly at the interhemispheric fissure. **E:** Graph showing the distance between the coronal suture and central sulcus starting above at the interhemispheric fissure and at every cm along their descent in 20 hemispheres (Table 2). As they run downward and lateral from the vertex, they converge to near where they cross the superior temporal line after which they diverge. The lower end of the central sulcus is closer to the coronal suture than the upper end. **F:** Graph showing the average inclination of the upper and lower halves of the coronal suture and central sulcus in comparison with the coronal plane passing through the upper end of their upper and lower halves in 20 hemispheres (Table 3). The central sulcus is steeper in the lower than the upper half. The opposite is true for the coronal suture, for which the upper half is steeper than the lower half. Cor. = coronal; Sag. = sagittal; Squam. = squamous; Sup. = superior; Temp. = temporal.

TABLE 2. Distance between the coronal suture and the anterior and posterior limits of the precentral gyrus starting at their upper ends and at every centimeter to their lower ends in 20 hemispheres*

	Anterior Limit		Posterior Limit	
Point	Mean (range)†	SD†	Mean (range)†	SD†
Upper end	3.6 (3.0–4.3)	0.4	5.3 (4.7–5.9)	0.4
1 cm	3.5 (2.4–4.4)	0.5	5.2 (4.5–6.0)	0.4
2 cm	3.5 (2.4–5.1)	0.6	5.1 (4.1–6.3)	0.6
3 cm	3.1 (2.3–4.2)	0.5	5.1 (4.2–5.7)	0.5
4 cm	2.6 (1.6–3.7)	0.6	4.8 (3.8–5.6)	0.5
5 cm	2.3 (1.4–3.5)	0.6	3.8 (2.8–4.7)	0.6
6 cm	1.8 (1.1–3.3)	0.6	3.6 (2.7–4.5)	0.5
7 cm	1.8 (0.6–3.3)	0.7	3.4 (2.3–4.3)	0.5
8 cm	1.9 (0.5–3.2)	0.8	3.4 (2.4–4.4)	0.6
9 cm	2.1 (1.2–3.2)	0.6	3.5 (2.4–4.3)	0.5
Lower end	2.3 (1.3–3.2)	0.6	3.8 (2.8–4.2)	0.4

* See Fig. 2E.
† Values are presented in centimeters.

arose from a stem artery with the posterior parietal artery and in 1 with the central artery.

Most Frequent Arterial Pattern

Medial Surface, Paracentral Lobule

The paracentral lobule is supplied predominantly by the paracentral artery with the superior parietal artery supplying the inferior and posterior margins.

Lateral Surface, Superior Third

The upper part of the lateral surface is supplied by the paracentral, posterior interior frontal, and superior parietal arteries, which arise on the medial surface. The lower part of the upper third is supplied by the central and anterior parietal arteries, which ascend from below (Figs. 3 and 5).

Lateral Surface, Middle and Inferior Thirds

These portions of the paracentral lobule are supplied predominantly by the central artery, except for small areas along the anterior and posterior margin, which are supplied by the precentral and anterior parietal arteries, respectively.

Venous Drainage

This study revealed considerable variability of drainage (Figs. 7 and 8). The drainage of the central lobe is usually directed to 1 or more of 3 sinuses—superior sagittal, transverse, and sphenoparietal—although in rare cases it may drain to the cavernous or inferior sagittal sinus.[39] The paracentral lobule and the upper two-thirds of the lateral surface frequently drain to the superior sagittal sinus. The lower third of the lateral surface most commonly drains to the superficial sylvian veins and from there to the transverse sinus via the vein of Labbé or anteriorly to the sphenoparietal sinus.

The anastomotic veins on the lateral surface that interconnect the drainage groups are the superficial sylvian vein and the veins of Labbé and Trolard (Fig. 7). The vein of Trolard, called the superior anastomotic vein, is the largest anastomotic vein. It crossed the lateral surface of the parietal and frontal lobes, connecting the superior sagittal sinus to the veins of the sylvian fissure. It frequently crossed the lateral surface as a central, precentral, or postcentral vein and could be duplicated as well. It was usually joined by other veins before emptying into the superior sagittal sinus. The vein of Labbé, also called the inferior anastomotic vein, crossed the temporal lobe connecting the superficial sylvian veins with the transverse sinus. It commonly began at the mid part of the sylvian fissure and ran posteriorly and inferiorly toward the anterior part of the transverse sinus (Fig. 7A and F). It can be a middle, anterior, or posterior temporal vein and can be a duplicate vein as well. The superficial sylvian vein ran along the sylvian fissure and drained anteriorly into the sinuses along the sphenoid ridge or posteriorly into the vein of Labbé, or both. It received several tributaries along its course (frontoparietal and temporosylvian veins) and usually emptied into the sphenoparietal sinus or, in 1 hemisphere, directly into the cavernous sinus. In rare cases it may continue posteriorly to drain into the superior petrosal sinus.[39]

Cortical Veins

The central lobe was drained by veins on both the me-

TABLE 3. Table showing the average angle of the upper and lower half of the coronal suture and central sulcus in comparison to the coronal plane passing through the upper end of their upper and lower halves in 20 hemispheres*

Microsurgical Structure	Mean (range)†	SD†
Coronal suture		
Upper end to midpoint of length	15.8 (12.1–21.1)	3.0
Midpoint of length to lower end	28.1 (24.0–34.2)	3.3
Central sulcus		
Upper end to midpoint of length	26.7 (19.3–32.5)	4.3
Midpoint of length to lower end	10.4 (1.5–15.9)	3.6

* See Fig. 2F.
† Values are presented in degrees.

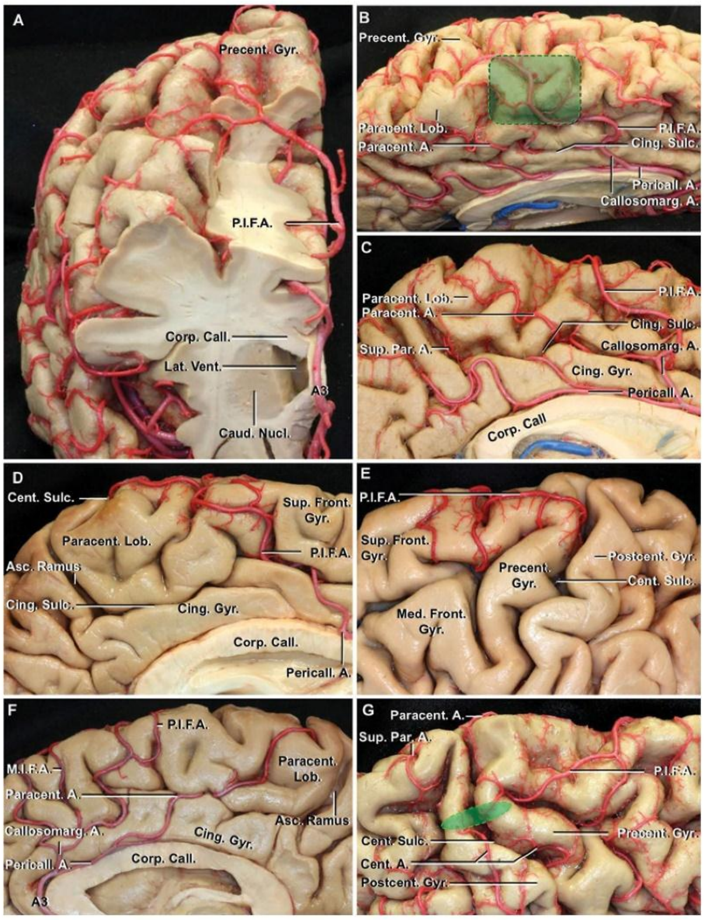

FIG. 3. A: The anterior part of the frontal lobe was removed using a coronal cut anterior to the foramen of Monro. The upper part of the superior frontal gyrus was removed to expose the course of the posterior internal frontal artery, which folds over the superior margin of the lateral surface approximately 1.5 cm anterior to the precentral gyrus after supplying the supplementary motor area. It also supplies the superior portion of the precentral gyrus on the lateral surface but not the paracentral lobule on the medial surface. **B:** The callosomarginal artery gives rise to the posterior internal frontal and paracentral arteries. The posterior internal frontal artery folds over the superior margin of the lateral surface and supplies the supplementary motor area *(green shaded area)* and the superior portion of the precentral gyrus. The paracentral artery courses inside the cingulate sulcus before turning upward to supply the paracentral lobule and a small portion of the upper part of the postcentral gyrus. Sacrificing these arteries may lead to a supplementary motor area syndrome with contralateral lower-limb weakness. **C:** An enlarged view of the paracentral lobule. The paracentral lobule is commonly supplied by the paracentral and superior parietal arteries. In this hemisphere the superior parietal artery is a branch of the pericallosal artery and runs in the ascending ramus of the cingulate sulcus to supply the lower and posterior borders of the paracentral lobule. The paracentral artery, a branch of the callosomarginal artery, courses in the cingulate sulcus and supplies the majority of the paracentral lobule. **D–G:** Other arteries have been removed to show the trajectory and area of supply of the left posterior internal frontal artery. **D:** Medial surface of left hemisphere. This posterior internal frontal artery arises from the pericallosal artery, runs upward and posterior to supply the posterior portion of the medial surface of the superior frontal gyrus. It folds over the superior margin of the hemisphere anterior to the paracentral lobule. **E:** Upper lateral surface of the left hemisphere shown in D. The posterior internal frontal artery folds around the superior border anterior to the central lobe to supply the posterior portion of the superior frontal gyrus and the upper part of the precentral gyrus. **F:** Medial surface of a right hemisphere. The callosomarginal artery arises from the precallosal segment of the pericallosal artery and gives rise to both the middle and posterior internal frontal arteries. The paracentral artery arises from the pericallosal artery and courses upward to reach the anterior part of the paracentral lobule. **G:** Superior part of the lateral surface of the right hemisphere shown in F. **FIG. 3** *(continued)*→

FIG. 3. G ***(continued)*****:** The watershed area between the ACA and MCA is located approximately 1.5 cm lateral to the superior margin of the lateral surface *(green shaded area)*, where there are anastomoses between branches of the MCA and ACA. The posterior internal frontal artery runs in an anterior to posterior direction. The watershed area is supplied by the central branches of the MCA and by the posterior internal frontal, paracentral, and superior parietal branches of the ACA. A. = artery; Callosomarg. = callosomarginal; Caud. = caudate; Lat. = lateral; Med. = medial; M.I.F.A. = middle internal frontal artery; Nucl. = nucleus; P.I.F.A. = posterior internal frontal artery; Pericall. = pericallosal; Vent. = ventricle.

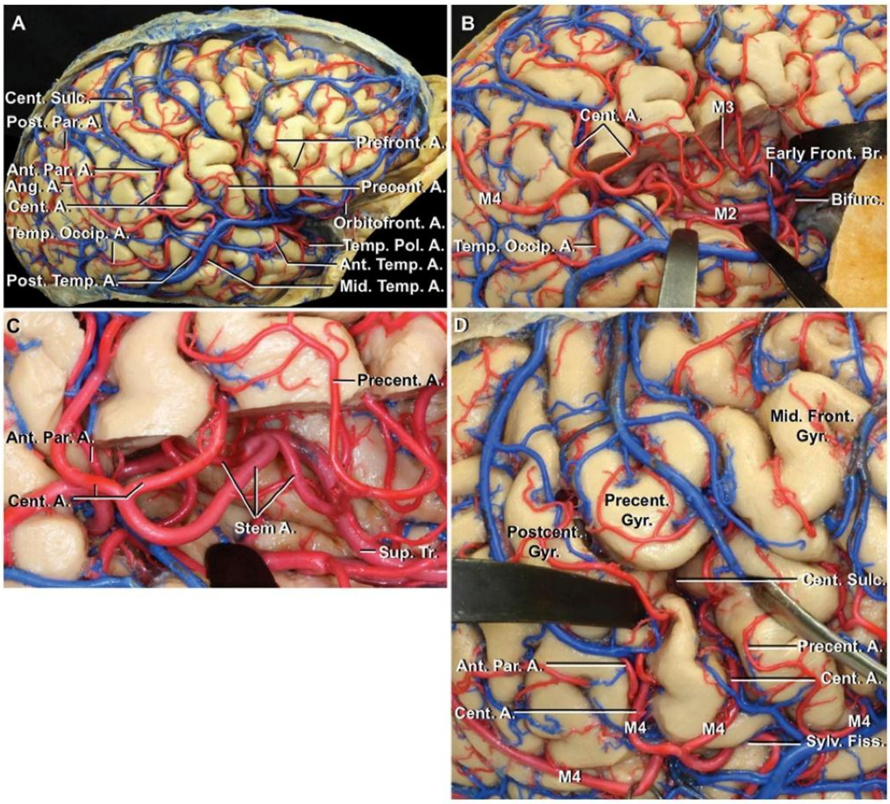

FIG. 4. A: Right cerebral hemisphere. The cortical distribution of the MCA includes most of the lateral surface of the hemisphere and all the insular and opercular surfaces. The cortical branches anastomose with the terminal branches of the ACA approximately 1.5 cm lateral to the superior border. The M_4, composed of the cortical branches of the MCA usually begins at the surface of the sylvian fissure and runs on the lateral surface commonly within the sulci. The cortical branches of the M_4 segment, named based on their supply to 12 different areas, are as follows: orbitofrontal, prefrontal, central, anterior parietal, posterior parietal, angular, temporooccipital, posterior temporal, middle temporal, anterior temporal, and temporopolar.[43] **B:** View of the M_2, M_3, and M_4 segments. The bifurcation occurs just proximal to the genu. The M_2 is constituted by the trunks that cross and supply the insula and end at the limiting sulci of the insula. The M_3 segment starts at or near the limiting sulci where the M_2 branches turn to course on the frontoparietal and temporal opercula. The M_4 segment is formed by the cortical branches. In this hemisphere the inferior trunk gives rise to the temporopolar, anterior temporal, middle temporal, posterior temporal, temporooccipital, angular and posterior parietal branches. An early frontal branch gives origin to the orbitofrontal and prefrontal arteries. The superior trunk gives rises to the precentral, central, and anterior parietal branches. **C:** Enlarged view. The cortical arteries that supply the central lobe can be followed from their origin on the postbifurcation trunks on the insular surface to the cortex. The superior trunk gives rise to 3 stem arteries from which the cortical branches arise. The anterior stem artery bifurcates into the precentral arteries that supply the lower portion of the precentral gyrus, and the large stem artery bifurcates and gives rise to 2 central arteries in what was found to be a frequent pattern. Another stem artery arose from the superior trunk as a single branch to become the anterior parietal artery. **D:** The central artery arises at the outer edge of the sylvian fissure as a double artery and supplies most of the central lobe. The precentral artery supplies the lower part of the precentral gyrus. The anterior parietal artery supplies the middle third of the posterior portion of the postcentral gyrus. Ang. = angular; Ant. = anterior; Ant. Par. = anterior parietal; Bifurc. = bifurcation; br. = branch; Fiss. = fissure; Orbitofront. = orbitofrontal; Post. = posterior; Prefront. = prefrontal; Sylv. = sylvian; Temp. Pol. = temporopolar; Temp. Occip. = temporooccipital; Tr. = trunk.

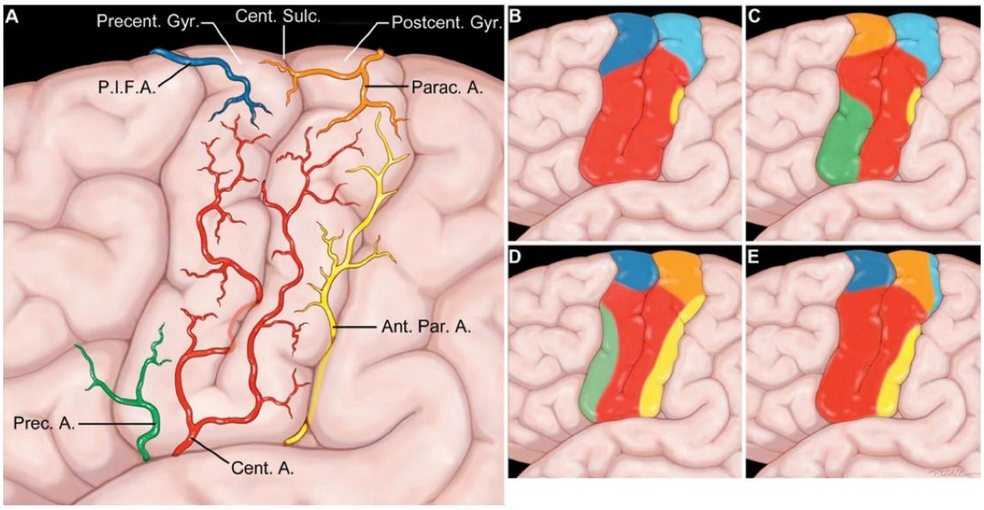

FIG. 5. A–E: Arterial supply of the lateral surface of the central lobe: posterior internal frontal artery *(dark blue)*, paracentral artery *(orange)*, superior parietal artery *(light blue)*, precentral artery *(green)*, central artery *(red)*, and anterior parietal artery *(yellow)*. **A:** Most common pattern. The posterior interior frontal and paracentral branches of the ACA supply the upper part. The majority of the lateral surface is supplied by the central branch of the MCA. The areas not supplied by the central artery are the anterior inferior part of the precentral gyrus supplied by the precentral and the posterior edge of the postcentral gyrus supplied by the anterior parietal artery. These cortical arteries often course in the sulci as well as on the surface of the gyri. **B–E:** Frequently encountered variations. **B:** The lower two-thirds of the central lobe is predominantly supplied by the central artery. On the superior third, the precentral gyrus is supplied by the posterior interior frontal artery and the postcentral gyrus by the superior parietal artery. **C:** The superior parts of the precentral and postcentral gyri are supplied by the paracentral and superior parietal arteries, respectively. There is no supply from the posterior inferior frontal artery. A larger than usual area of the precentral gyrus is supplied by the precentral artery. **D:** The precentral and the anterior parietal arteries have a larger than usual area of supply that narrows the large proximal area usually supplied by the central artery. The superior third is supplied by the posterior internal frontal and paracentral arteries. **E:** There is no contribution from the precentral artery. The anterior parietal artery supplies the lower two-thirds of the posterior part of the postcentral gyrus. The area supplied by the cortical branches of the ACA is divided between the posterior interior frontal, paracentral, and superior parietal arteries. Parac. = paracentral; Prec./Precent. = precentral. Copyright Albert L. Rhoton Jr. Published with permission.

dial and lateral surface of the hemisphere. The veins on the lateral surface could empty into ascending or descending groups (Figs. 7 and 8).[39]

Lateral Surface, Ascending Group

The central vein usually drained the largest portion of the central lobe, even reaching the lower portion in some cases. It drained all or part of the pre- and postcentral gyri in 90% of hemispheres. The precentral vein usually drained the anterior portion of the precentral gyrus. It drained the precentral gyrus in 14 hemispheres and the postcentral gyrus in 1 hemisphere. The postcentral vein is the one most commonly connecting both the sagittal sinus and superficial sylvian vein to form a vein of Trolard. It drained the posterior part of the postcentral gyrus and most commonly emptied into the superior sagittal sinus. The postcentral vein drained the postcentral gyrus in 15 hemispheres. It did not drain the precentral gyrus in any hemisphere.

The middle and posterior frontal veins infrequently drain the central lobe and in this study drained the precentral gyrus in only 1 hemisphere each. The anterior parietal vein usually drains the angular and supramarginal gyri and in this study drained the postcentral gyrus in 2 hemispheres.

Lateral Surface, Descending Group

The frontosylvian veins drained the frontal operculum and emptied into the superficial sylvian veins. They drained the precentral gyrus in 18 hemispheres and the postcentral gyrus in 1 hemisphere. The parietosylvian veins drained the postcentral gyrus and emptied into the superficial sylvian veins in 15 hemispheres. In 4 hemispheres the postcentral gyrus was drained directly by the vein of Trolard.

Medial Surface

The medial posterior frontal vein drained the medial frontal lobe and the cingulate gyrus above the genu of the corpus callosum. It drained the anterior margin of the paracentral lobule in 1 hemisphere. The paracentral vein drained the anterior portion of the paracentral lobule in all hemispheres and the posterior portion in 15. It emptied

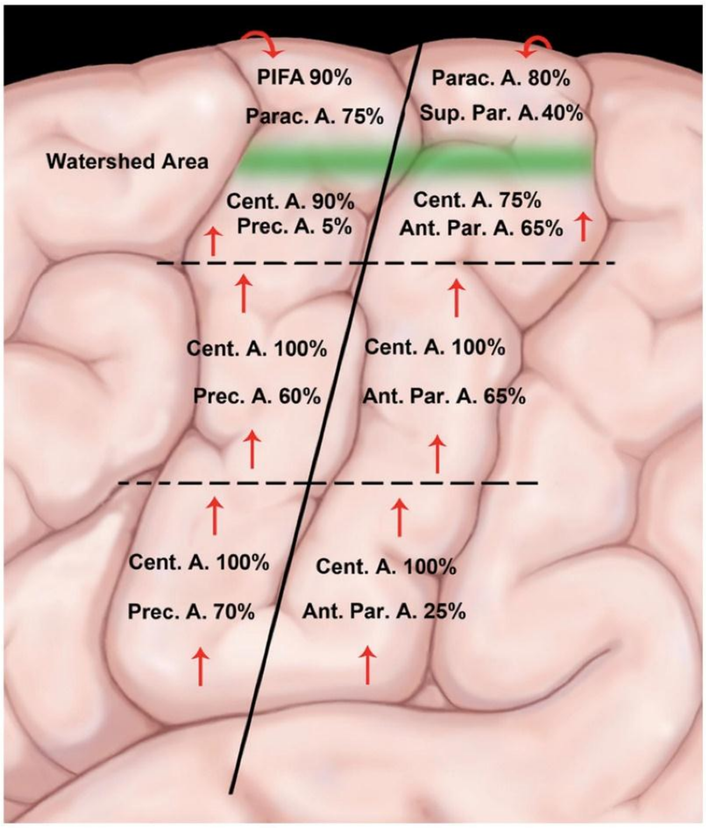

FIG. 6. Illustration showing the percentage of cortical branches of the ACA and MCA that supply the upper, middle, and lower thirds of the central lobe. The watershed area between the ACA and MCA is located approximately 1.5 cm lateral to the superior margin *(green shaded area)*. The branches of the MCA (central, precentral, and anterior parietal arteries) arise near the surface of the sylvian fissure and ascend to anastomose with the descending cortical branches of the ACA (posterior interior frontal, paracentral, and superior parietal arteries), which fold around the superior margin. Copyright Albert L. Rhoton Jr. Published with permission.

into the superior sagittal sinus. In 4 hemispheres the drainage of the paracentral lobule was exclusively through the paracentral veins. The anteromedial parietal vein drained the posterior part of the paracentral lobule in 15 hemispheres and the anterior part in 3 hemispheres. It emptied into the superior sagittal sinus or into a large cortical vein on the lateral surface. It usually drains the precuneus.

Sinus Drainage

In 19 of 20 hemispheres, the superior two-thirds of the paracentral lobule drained to the superior sagittal sinus (Figs. 7 and 8). In 2 hemispheres the middle third of the postcentral gyrus drained to the transverse sinus. The inferior third of the precentral gyrus drained to the sphenoparietal sinus in 10 hemispheres, to the transverse sinus via the vein of Labbé in 8, and to the superior sagittal sinus in 2. The lower portion of the postcentral gyrus drained to the sphenoparietal sinus in 7, the transverse sinus in 9, and to the superior sagittal sinus via the vein of Trolard in 4 hemispheres.

The vein of Trolard contributed to the venous drainage of the central lobe in 15 hemispheres. It was located at the site of the postcentral vein in 8, central vein in 3, precentral vein in 2, anterior parietal vein in 1, and was duplicated in 1 hemisphere where it was located at the site of the precentral and central veins.

Most Common Drainage Pattern

Medial Surface

The majority of the paracentral lobule drained through

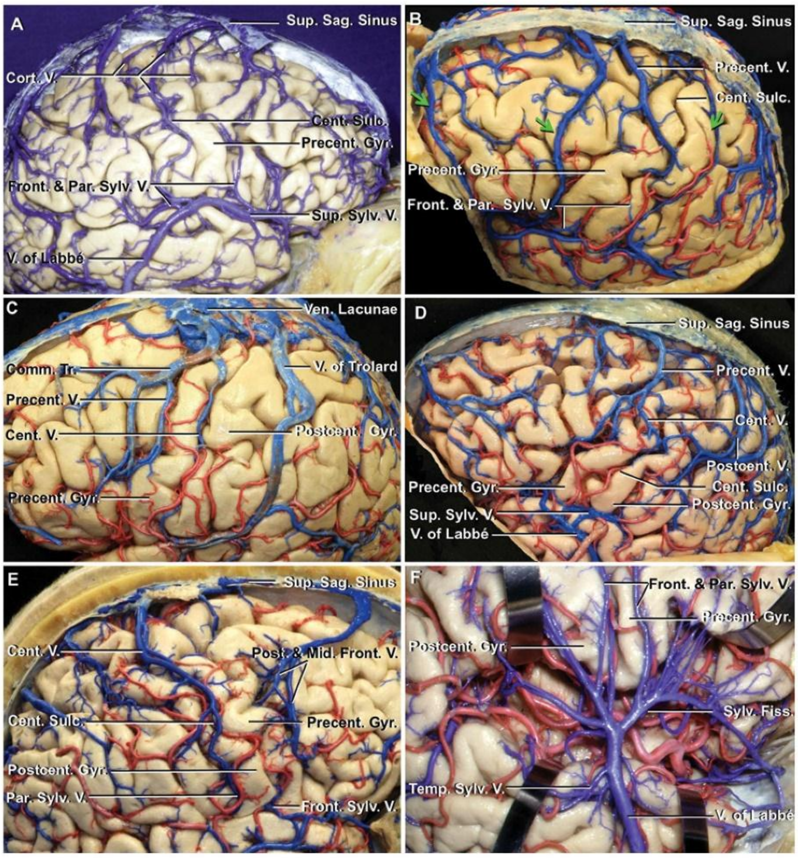

FIG. 7. A–F: Venous drainage of the central lobe. **A:** A common pattern of drainage. The superior two-thirds of the right hemisphere is drained by the cortical veins emptying into the superior sagittal sinus. The inferior third drains through the frontosylvian and parietosylvian veins to a superficial sylvian vein that empties into a large vein of Labbé and the transverse sinus. **B:** Three veins of Trolard *(green arrows)* crossed this left hemisphere, connecting the superficial sylvian vein with the superior sagittal sinus. The posterior part of the central lobe is drained through the posterior vein of Trolard. A precentral vein drains a large portion of the central lobe. The inferior third is drained by the frontosylvian and parietosylvian veins, except for the anterior part of the precentral gyrus, which drains through the middle anastomotic vein of Trolard. **C:** A large common trunk receives drainage from several cortical veins before passing below a large venous lacuna to empty into the superior sagittal sinus. The majority of the posterior right central lobe is drained by central and precentral veins that pass below this lacuna. The posterior part of the central lobe drains to the superior sagittal sinus through a large anastomotic vein of Trolard. **D:** A large precentral vein drained the majority of the superior two-thirds of the precentral gyrus. The central vein drained a portion of the precentral gyrus and emptied into the larger precentral vein that emptied into the superior sagittal sinus. The inferior third of the central lobe drained into a hypoplasic superficial sylvian vein joined to a vein of Labbé that emptied into the transverse sinus. The superior two-thirds of the postcentral gyrus is drained by a postcentral vein that empties into the superior sagittal sinus. **E:** The right central lobe is drained predominantly by a large central vein that empties into the superior sagittal sinus. A small portion of the anterior edge of the precentral gyrus is drained by the posterior and middle frontal veins that form a common trunk before emptying into the superior sagittal sinus. The lower portion of the central lobe is drained by frontosylvian and parietosylvian veins that empty into the superficial sylvian vein. **F:** Enlarged view of the opercular region of another right hemisphere. The lower portion of the central lobe is drained by frontosylvian and parietosylvian veins that empty into a superficial sylvian vein that emptied predominantly through a large vein of Labbé into the transverse sinus. Comm. = communicating; Cort. = cortical; V. = vein; Ven. = venous.

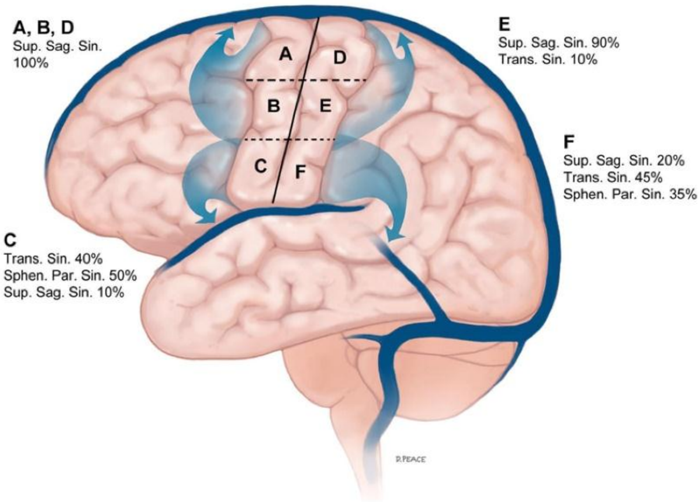

FIG. 8. Dominant drainage pathways of different parts of the central lobe. *A*, *B*, and *C* are respectively the upper, middle, and lower thirds of the precentral gyrus, and *D*, *E*, and *F* are the upper, middle, and lower thirds of the postcentral gyrus. Parts *A*, *B*, and *D* drain to the superior sagittal sinus in 100% of the hemispheres. Parts *C* and *F* drain predominantly to the sphenoparietal and transverse sinuses with a slightly higher proportion of the precentral gyrus draining to the sphenoparietal and the postcentral gyrus to the transverse sinus. In some hemispheres the lower third drained to the superior sagittal sinus due to the presence of a large vein of Trolard that drained predominantly upwards. The most common location of the vein of Trolard was along the territory drained by the postcentral vein. In 10% of the hemispheres, area *E* drained to the transverse sinus due to the presence of larger than average parietosylvian veins. Sin. = sinus; Sphen. Par. = sphenoparietal; Trans. = transverse. Copyright Albert L. Rhoton Jr. Published with permission.

the paracentral vein to the superior sagittal sinus. The area drained by this vein covers the anterior half and the anterior two-thirds of the posterior half. The posterior margin and the posterior half of the inferior margin of the paracentral lobule drained through the anteromedial parietal vein, which emptied into the superior sagittal sinus.

Lateral Surface

The superior third drained mainly upward through the central vein to the superior sagittal sinus. The postcentral vein commonly drained the posterior margin of the postcentral gyrus (Fig. 8). The middle third drained predominantly to the superior sagittal sinus through the central vein. However, the anterior and posterior margins of the central lobe were drained by the pre- and postcentral veins, respectively. The precentral veins curved anteriorly as they ascended and thus frequently did not contribute to the drainage of the superior third of the central lobe. At the junction between the middle and inferior third, there was usually a change in the drainage direction. The inferior third drained downward to empty into the superficial sylvian veins and from there to the transverse sinus (via vein of Labbé) or to the sphenoparietal sinus (via the superficial sylvian veins). The frontosylvian veins drained the precentral gyrus and the parietosylvian veins drained the postcentral gyrus.

Discussion

Advances in microsurgical techniques, modern neuroimaging, neuronavigation systems, and cortical mapping have made surgery in the central lobe safer. However, knowledge of the anatomy remains an essential tool for performing safe and accurate approaches to the central lobe.

Craniometric Features

Broca[10,11] was the first to describe the relationship of the coronal suture with the central sulcus in 1861 and was the first to perform a craniotomy oriented by cranial topography. The coronal suture is easily palpable through the scalp and provides valuable information, as seen on CT and MR images, that is easily transferable to the surgical field.

The coronal suture and central lobe have a fairly constant relationship. They run somewhat parallel, but the separation between the coronal suture and the precentral gyrus is less pronounced at their lower end than at their upper end bordering the superior sagittal sinus.[10,11,17,21–23,40,46] However, the closest point between the coronal suture and the precentral and central sulci was found to be the point at or near where the superior temporal line crosses the coronal suture.

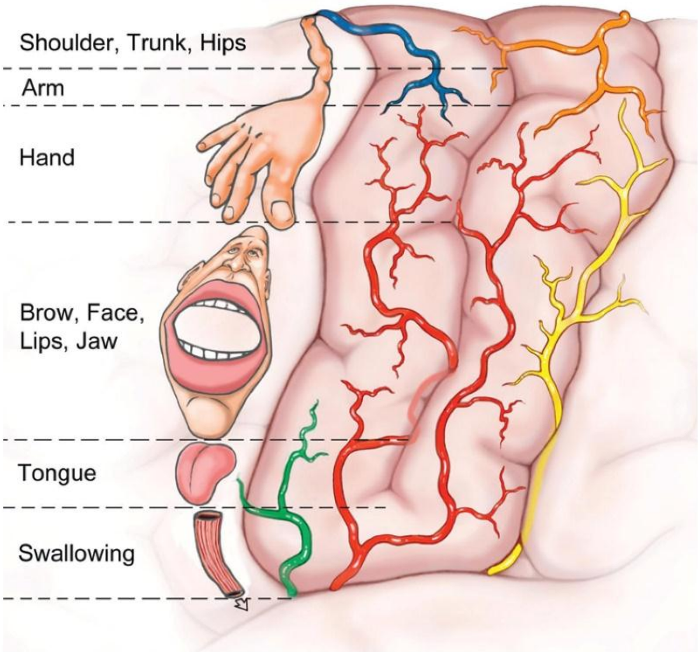

FIG. 9. Diagram of the left hemisphere showing the correlation of the most common pattern of central lobe arterial supply to the classic homunculus on the lateral surface. The cortical areas supporting fine movements are disproportionally large in comparison with areas supporting more gross movements. Obliteration of a single arterial branch may lead to a motor or sensory deficit in a specific part of the body. See Fig. 5 for legend for arteries on pre- and postcentral gyri. Copyright Albert L. Rhoton Jr. Published with permission.

Neural Features

Although there is considerable variability in sulcal and gyral anatomy surrounding the central lobe, close inspection reveals a relatively constant basic organization. The development of refined microsurgical techniques such as transsulcal approaches established the sulci and gyri as fundamental landmarks of the cerebrum.[45] The cortex of the central lobe has very specific functional localization. Therefore, it is essential to correctly identify sulci and gyri on preoperative imaging studies when operating in the region and to understand that lesions causing significant mass effect may distort normal topography and landmarks. Recent studies have shown that a greater extension of glioma resection is a statistically significant predictor of progression-free survival and length of survival.[5,8,13,15,16,25,27,30–32,34,35,47–49] Therefore, radical resection should be pursued but not at the expense of patients' quality of life. This strategy minimizes the risk of misdiagnosis, relieves the symptoms of mass effect, and can improve neurological deficits due to compression of the central lobe. To accomplish this, an understanding of gyral and sulcal anatomy is essential. Currently, eloquent sensorimotor cortex identification based on topographical and radiological anatomy is combined with functional MRI and direct electrical cortical stimulation.[6,18,26,29,33,37,50,55]

The authors of several studies on mapping the sensorimotor cortex have reported that despite having a common general organization, variations in the somatotopy are frequently found.[2,6,7,18,26,29,33,37,38,52,53,55] They suggest that Penfield's homunculus be used as a simplified teaching tool but not as an accurate map (Fig. 9).[2,18,38,52,53] Two groups have reported sensorimotor function outside the central lobe.[5,55] These studies suggested that the primary motor cortex may extend beyond the anterior edge of the precentral gyrus. Berger and Hadjipanayis[5] found that the lowest threshold for electrical stimulation–induced movements of the body was on the precentral gyrus. When stimulating the premotor cortex, the threshold was higher, and the movements were slower and likely to involve larger groups of muscles. These findings may explain the transient motor deficits reported following resection of the area anterior to the precentral gyrus.

Berger and colleagues[5,13,27,48,49] have also reported on the importance of cortical mapping to delineate the motor cortex to achieve the greatest resection possible and to improve the prognosis in glioma surgery. Robles and colleagues[47] reported that radical resection of low-grade gliomas without preserving any margin around eloquent structures, such as the precentral gyrus, can be safely performed using subpial excision up to the edge of the arachnoid covering the adjacent eloquent gyrus. Martino et al.[30] demonstrated that radical glioma resections in eloquent areas of the brain, despite causing transient deficits in the immediate postoperative period, were associated with a decrease in morbidity over medium- and long-term periods and a longer preservation of the patient's professional life. Chang et al.[14] reported approaching cavernous malformations deep to the precentral gyrus obliquely through the premotor cortex while avoiding damage to cortical arteries. An understanding of sulcal, gyral, and arterial anatomy is essential to perform these resections safely and accurately.

Arterial Supply

When operating in the central lobe, it is important to remain constantly aware of the position of the arterial supply because of the severe deficits that may follow their occlusion. Gempt et al.[20] reported that neurological impairment following glioma resection was more frequently due to ischemic lesions than to cortical or subcortical structural damage. When performing surgeries involving the medial surface of the frontal lobe, care must be taken to avoid coagulating posteriorly directed branches of the pericallosal and callosomarginal arteries. Coagulation of these branches, although at a distance from the central lobe, may lead to motor weakness more prominent in the contralateral foot and leg than in the upper limb. Sensory loss, usually transient, is another consequence of infarctions of the supplementary motor area. Urinary incontinence occurs in the acute phase after bilateral occlusion.

Chaddad-Neto et al.[12] reported that arteriovenous malformations (AVMs) of the central lobe are suitable for surgical treatment in selected cases based on neurological status, AVM grade, patient age, and so on. The first steps are to open all the sulci adjacent to the lesion and to identify and differentiate the feeding arteries from arterialized veins. If this differentiation is not sufficient with the microscope, temporary clipping may help. If temporarily clipped, a feeding artery will collapse between the clip and the nidus, and an arterialized vein will tumesce between the clip and the nidus. AVMs of the central lobe on the lateral surface usually receive feeders from the M_4 cortical branches. It is important to be sure that the artery being obliterated ends in the AVM and is not a "passing through" artery that supplies brain tissue distal to the AVM, while remembering that "passing through" arteries may feed the AVM through small lateral branches that must be carefully dissected and obliterated while preserving the main arterial trunk.[3] AVMs on the medial surface receive feeders from branches of the ACA. AVMs adjacent to the superior border will, most likely, receive feeders from both the MCA and the ACA. After obliteration of the AVM's feeders, circumferential dissection of the nidus and transection of the draining veins is then performed.

Venous Drainage

Sacrifice of individual cortical veins does not usually lead to venous infarction, brain swelling, hemorrhage, or neurological deficits because of the abundant anastomoses between veins draining adjacent cortical areas. There are also anastomoses at the superior border of the hemispheres between the veins draining adjacent parts of the lateral and medial surface of the central lobe. These anastomoses are located at the terminal ends of the veins just proximal to where the bridging veins enter the superior sagittal sinus. However, the sacrifice of a major venous trunk should be avoided, either by working around it or dividing some smaller tributaries that will allow the major trunk to be displaced out of the surgical field. Care should be taken to avoid damage to bridging veins if they appear larger than normal, because the risk of venous infarction increases as the veins increase in size. In some cases a large vein of Trolard will drain the majority of the central lobe. Obliteration of such a vein can lead to venous infarction with severe deficits. As a result of the arterial supply to the infarcted tissue not being compromised, capillary hypertension and hemorrhagic transformation is common and is typically heterogeneous and gyriform.

When operating in the parasagittal area, an attempt must be made to preserve the sinuses coursing in the dura lateral to the superior sagittal sinus, which frequently receives the terminal end of several cortical veins before emptying into the superior sagittal sinus. Obliteration of the bridging veins from the central lobe that empty into the superior sagittal sinus may cause contralateral hemiparesis more prominent in the lower limbs and usually transient.[39]

Conclusions

Despite some variability, there are common patterns in gyral and sulcal configuration, craniometric relationships, arterial supply, and venous drainage that can create a road map for approaching pathologies in the central lobe.

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Author Contributions

Conception and design: Rhoton, Frigeri, Paglioli. Acquisition of data: Rhoton, Frigeri, Paglioli. Analysis and interpretation of data: Rhoton, Frigeri. Drafting the article: Rhoton, Frigeri. Critically revising the article: Rhoton, Frigeri, Paglioli. Reviewed submitted version of manuscript: Rhoton, Frigeri, Paglioli. Approved the final version of the manuscript on behalf of all authors: Rhoton. Statistical analysis: Rhoton, Frigeri. Administrative/technical/material support: Rhoton. Study supervision: Rhoton. Provided training in microsurgical anatomy: de Oliveira.

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DISCUSSÃO – ARTIGO 2

O artigo intitulado “Microsurgical Anatomy of the Central Lobe” publicado no Journal of Neurosurgery em 2015 consiste num estudo anatômico da região central do cérebro feito pelo autor no laboratório de Neuroanatomia cirúrgica da Universidade da Flórida nos EUA.

Neste estudo original foram descritos os principais aspectos anatômicos relevantes (anatomia giral, relações craniométricas, suprimento arterial e drenagem venosa) da região central do cérebro e adjacências. A região central do cérebro é constituída pelos giros central e pós central, na linha média é representada pelo lóbulo paracentral. A região é origem das fibras motoras e adjacente à área motora suplementar caudal, fundamentais na gênese das crises de queda. Os giros pré e pós-centrais e o lóbulo paracentral têm uma anatomia morfológica e funcional que os diferencia do restante de seus respectivos lóbulos e são considerados por muitos como um único lobo. Um completo entendimento das relações anatômicas do lobo central é essencial no planejamento pré-operatório e no estabelecimento marcos intraoperatórios confiáveis.

ANEXO 3 – CARTA DE APROVAÇÃO COMISSÃO CIENTIFICA

S I P E S Q

Sistema de Pesquisas da PUCRS

Código SIPESQ: 8638

Porto Alegre, 17 de abril de 2018.

Prezado(a) Pesquisador(a),

A Comissão Científica da ESCOLA DE MEDICINA da PUCRS apreciou e aprovou o Projeto de Pesquisa "VALOR PREDITIVO DA TRACTOGRAFIA E DO EEG PÓS OPERATÓRIO EM PACIENTES SUBMETIDOS A CALOSOTOMIA POSTERIOR SELETIVA".

Atenciosamente,

Comissão Científica da ESCOLA DE MEDICINA

ANEXO 4 – APROVAÇÃO CEP

PONTIFÍCIA UNIVERSIDADE
CATÓLICA DO RIO GRANDE
DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: VALOR PREDITIVO DA TRACTOGRAFIA E DO EEG POS OPERATORIO EM PACIENTES SUBMETIDOS A CALOSOTOMIA POSTERIOR SELETIVA

Pesquisador: Andre Luis Fernandes Palmini

Área Temática:

Versão: 1

CAAE: 87914318.6.0000.5336

Instituição Proponente: UNIAO BRASILEIRA DE EDUCACAO E ASSISTENCIA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.612.300

Apresentação do Projeto:

As epilepsias de difícil controle constituem um desafio na pratica neurológicaÉ uma condição estigmatizante, e com efeito devastador na vida do paciente, sua família e seu círculo social.A evolução medicamentosa através das pesquisas nas universidades e na indústria farmacêutica, proveram aos neurologistas um grande arsenal terapêutico no tratamento das epilepsias ditas refratarias. As novas drogas, porém, não foram capazes de eliminar esta condição. A evolução no tratamento desta condição teve um grande salto quando no final da década de 80 o tratamento cirúrgico das epilepsias foi de novo lembrado como uma possibilidade terapêutica plausível.Os novos e modernos métodos diagnósticos, principalmente a RNM (ressonância nuclear magnética), permitiram que o campo da cirurgia da epilepsia se se desenvolve exponencialmente. O tratamento cirúrgico das epilepsias é hoje consagrado, apesar de ainda ser subutilizado devido a uma série de fatores.Dentre os tratamentos possíveis a serem realizados, podemos dividir as opções entre dois grandes grupos:1- ressectivos ou curativos2- desconectivos ou paliativosO presente trabalho enfoca no segundo grupo. A calosotomia posterior seletiva têm sido amplamente usadas em pacientes com epilepsias refratarias que sofrem de crises súbitas de atonia (drop attacks). A melhora dos pacientes com este tipo de crise após serem submetidos ao procedimento cirúrgico supracitado, é dramática. Porém, um pequeno subgrupo de pacientes não apresenta uma melhora tão significativa.Diante das evidencias clinicas de bons resultados e da falta de dados que justifiquem um pior controle de crises, esse trabalho visa descobrir e descrever

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os fatores relacionados a menores índices de sucesso do procedimento.

Objetivo da Pesquisa:

Objetivo primário:

Associar os achados dos exames complementares pós-operatórios (RNM, tractografia e EEG) com o desfecho clinico dos pacientes operados.

Objetivo Secundário:

1. Determinar se o coeficiente de ressecção do corpo caloso tem uma influência favorável no desfecho2. Associar a presença de fibras do corpo caloso oriundas das regiões motoras e pré motoras com a persistência de crises epiléticas do tipo drop attack no pós-operatório3. Determinar se a presença e quantidade de bissincronismos secundários no EEG pós-operatório estão associados a uma menor taxa de melhora clínica.

Avaliação dos Riscos e Benefícios:

Riscos:

O PROJETO APRESENTA RISCO MÍNIMO PARA OS PARTICIPANTES

Benefícios:

DETERMINAR FATORES PROGNÓSTICOS EM PACIENTES PORTADORES DE EPILEPSIA DE DIFÍCIL CONTROLE SUBMETIDOS A CALOSOTOMIA POSTERIOR SELETIVA

Comentários e Considerações sobre a Pesquisa:

No programa de cirurgia da epilepsia de Porto Alegre, localizado no Hospital São Lucas da PUCRS, os pacientes candidatos ao procedimento, são submetidos a uma ressecção seletiva dos dois terços posteriores do corpo caloso. Tendo como resultado, uma melhora clínica
significativa com diminuição drástica ou cessação das crises de atonia e também no número e intensidade dos outros tipos de crise epilética. Assim, é possível que este estudo traga ainda mais benefícios aos pacientes.

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos foram apresentados.

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Considerações Finais a critério do CEP:

Diante do exposto, o CEP-PUCRS, de acordo com suas atribuições definidas nas Resoluções n° 466 de 2012 e Norma Operacional n° 001 de 2013 do Conselho Nacional de Saúde, manifesta-se pela aprovação do estudo.

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Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	lattes.pdf	18/04/2018 16:05:31	Denise Cantarelli Machado	Aceito
Orçamento	orcamento.pdf	18/04/2018 16:05:15	Denise Cantarelli Machado	Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1115959.pdf	17/04/2018 20:49:53		Aceito
Outros	aprovacao.pdf	17/04/2018 11:38:40	Andre Luis Fernandes Palmini	Aceito
Outros	docunificado.pdf	17/04/2018 11:38:17	Andre Luis Fernandes Palmini	Aceito
Projeto Detalhado / Brochura Investigador	projeto.pdf	17/04/2018 11:29:23	Andre Luis Fernandes Palmini	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCUD.pdf	17/04/2018 11:28:43	Andre Luis Fernandes Palmini	Aceito
Outros	Carta.pdf	17/04/2018 11:27:35	Andre Luis Fernandes Palmini	Aceito
Outros	Encaminhamento.pdf	17/04/2018 11:26:34	Andre Luis Fernandes Palmini	Aceito
Folha de Rosto	Folha.pdf	17/04/2018 11:25:51	Andre Luis Fernandes Palmini	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 20 de Abril de 2018

Assinado por:
Paulo Vinicius Sporleder de Souza
(Coordenador)

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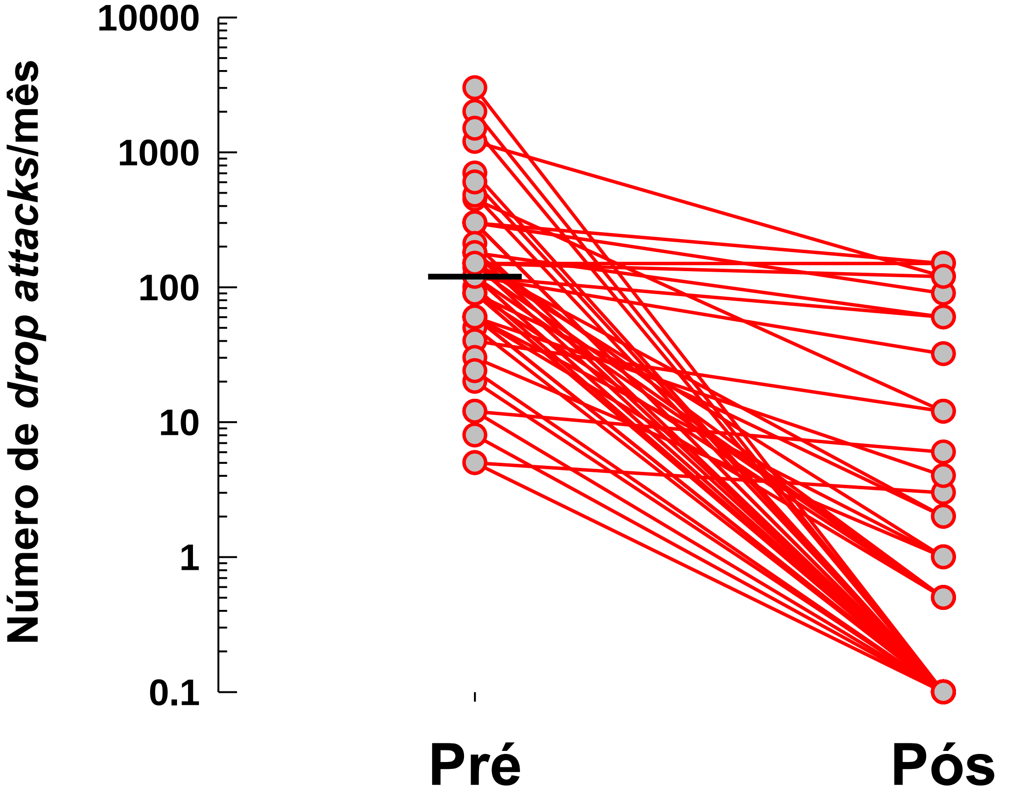
APÊNDICE

APÊNDICE 1 - FIGURAS DOC



	Pré	Pós
mediana	120	0
P25 – P75	60 – 300	0 - 3
mín - máx	5 – 3000	0 - 150

Fig1. Gráfico em forma de log, com dados individuais da frequência de crises de drop attacks antes e após calosotomia seletiva posterior em 51 pacientes. *A forma logarítmica foi necessária pois alguns pacientes apresentavam mais de 3 mil crises de queda por mês*.

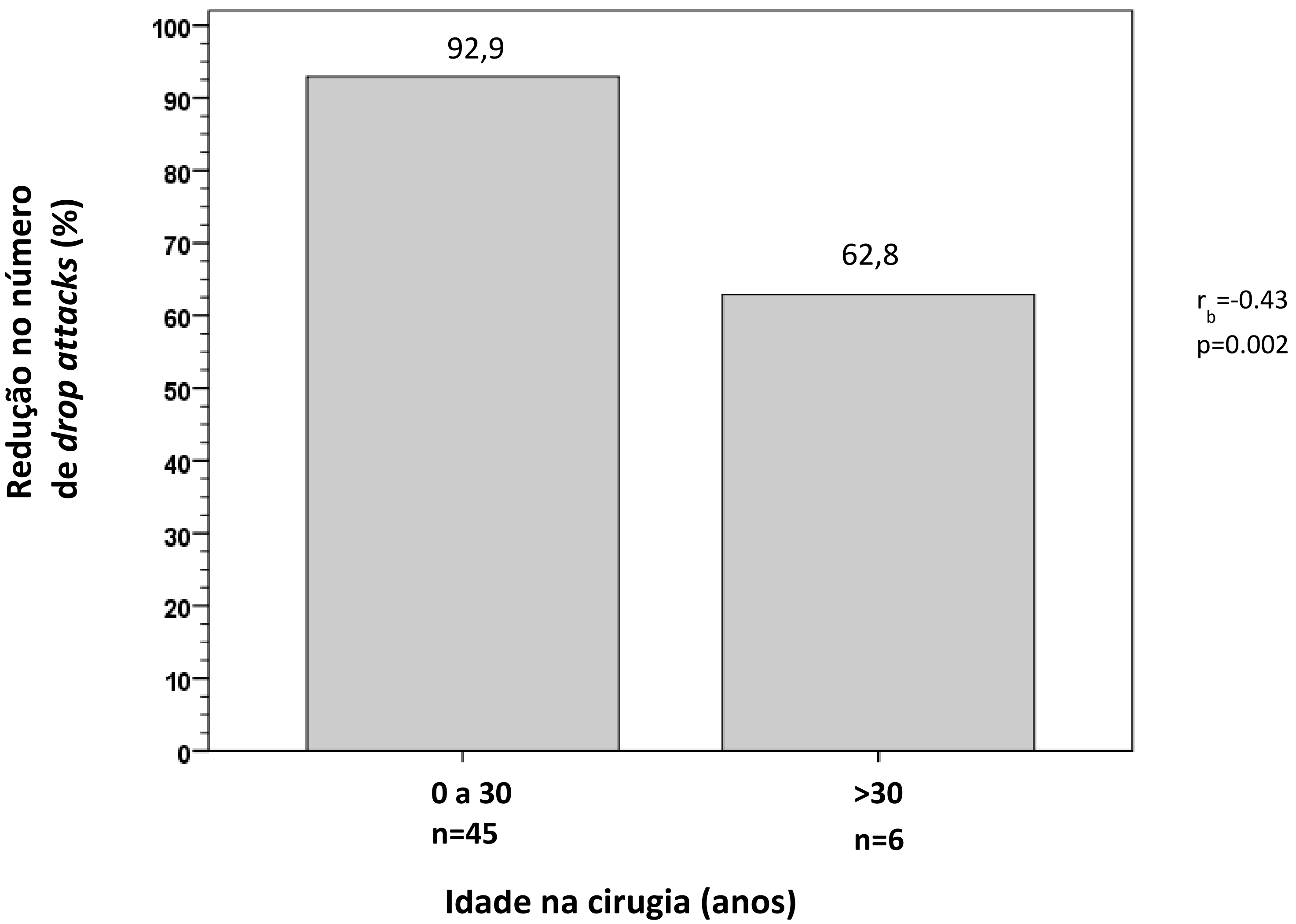


Fig. 2 Redução no número de drop attacks nos pacientes com até 30 anos de idade (coluna 1) vs. Redução nos pacientes com mais de 30 anos (coluna 2).

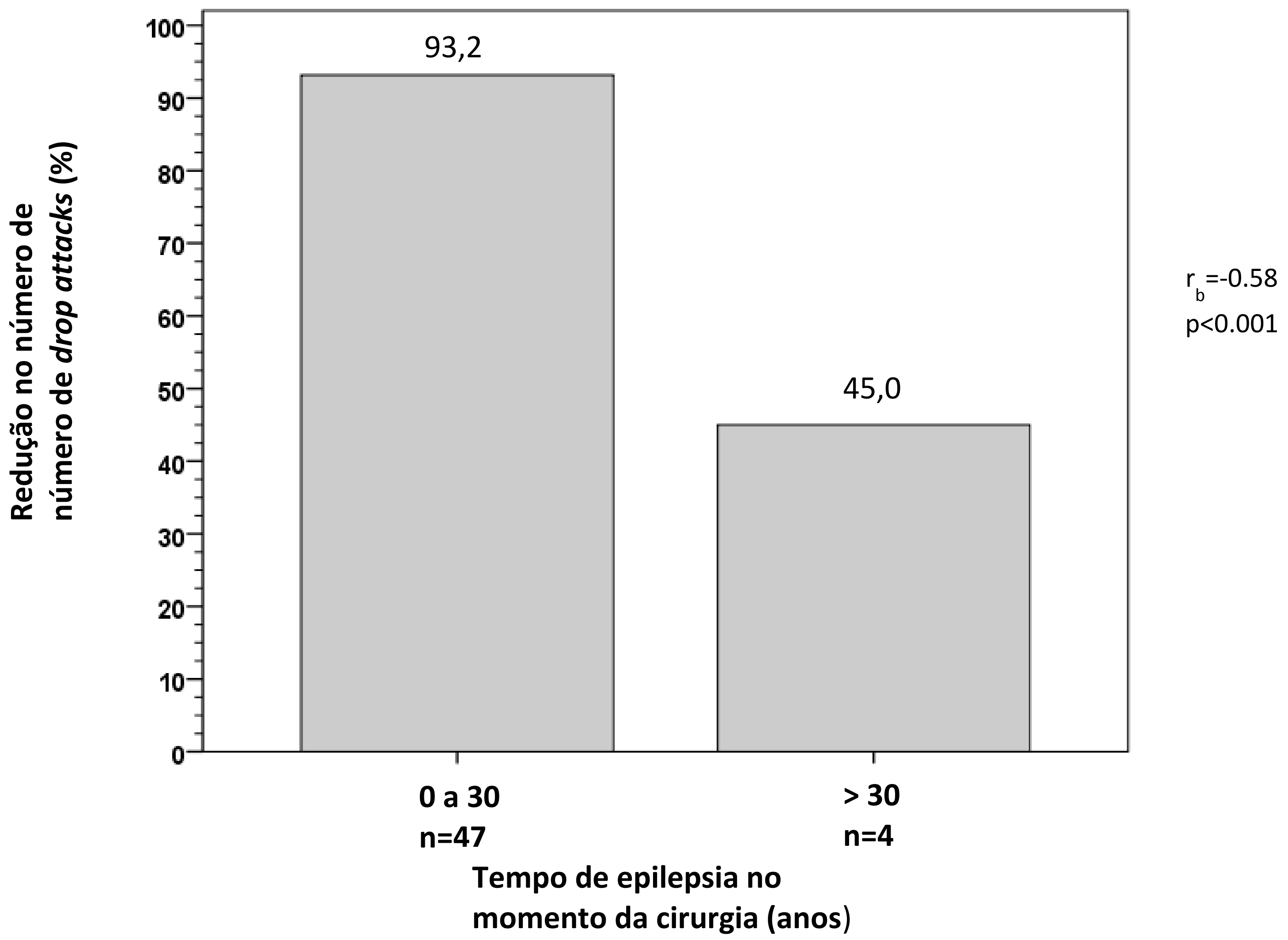


Fig. 3 Redução no número de drop attacks nos pacientes com até 30 anos de epilepsia (coluna 1) vs. redução nos pacientes com mais de 30 anos (coluna 2) .

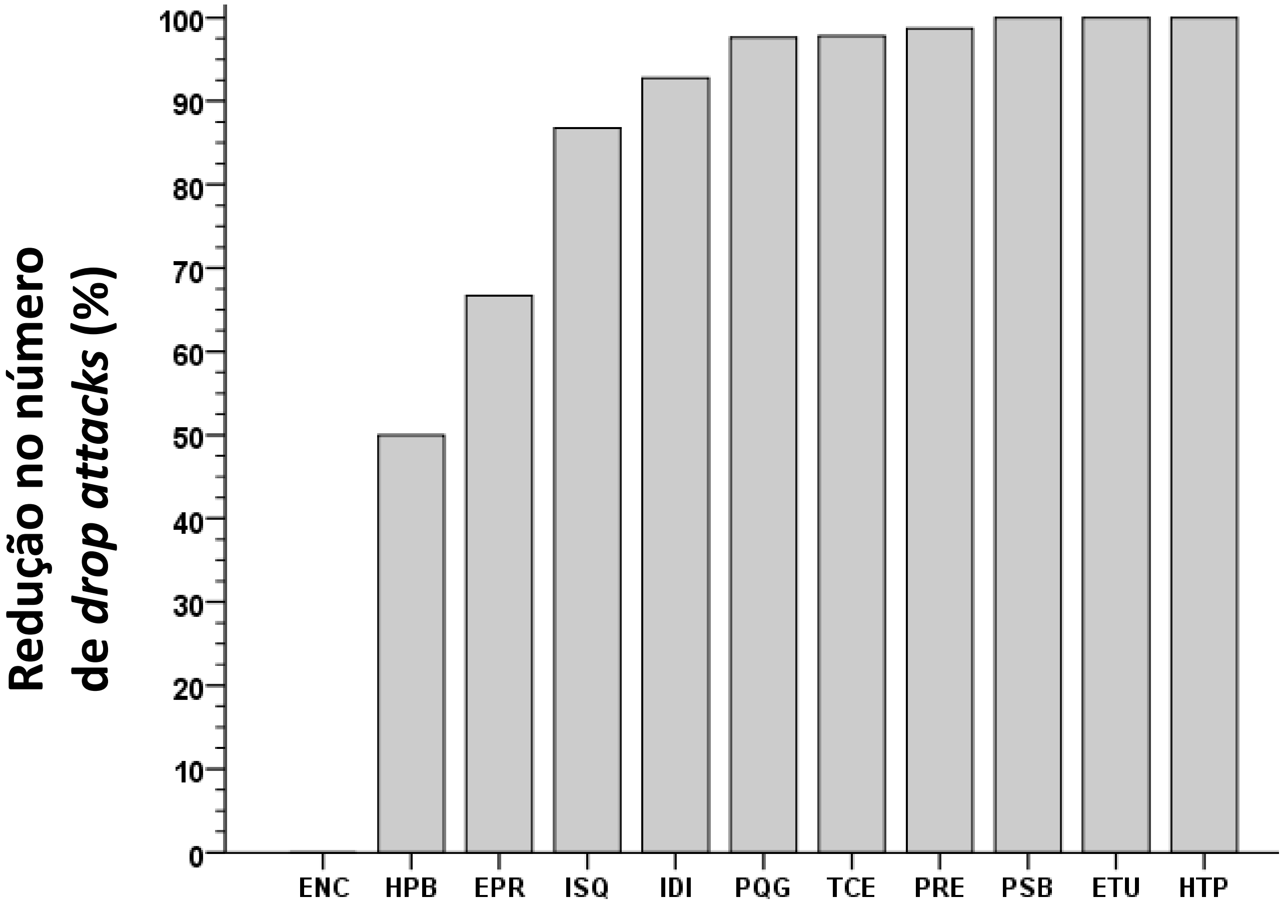


Fig. 4 Redução no número de drop attacks nos diferentes grupos etiológicos. *Onde: ENC: Encefalite; HPB: Heterotopia periventricular bilateral; EPR: Encefalopatia pós radioterapia; ISQ: Lesão hipóxico-isquêmica perinatal; IDI: Desconhecida; PQG: Paquigiria TCE: Sequela de traumatismo craniano; PRE: Prematuridade PSB: Polimicrogiria perisilviana bilateral ETU: Esclerose tuberosa HTP: Heterotpia periventricular unilateral.*

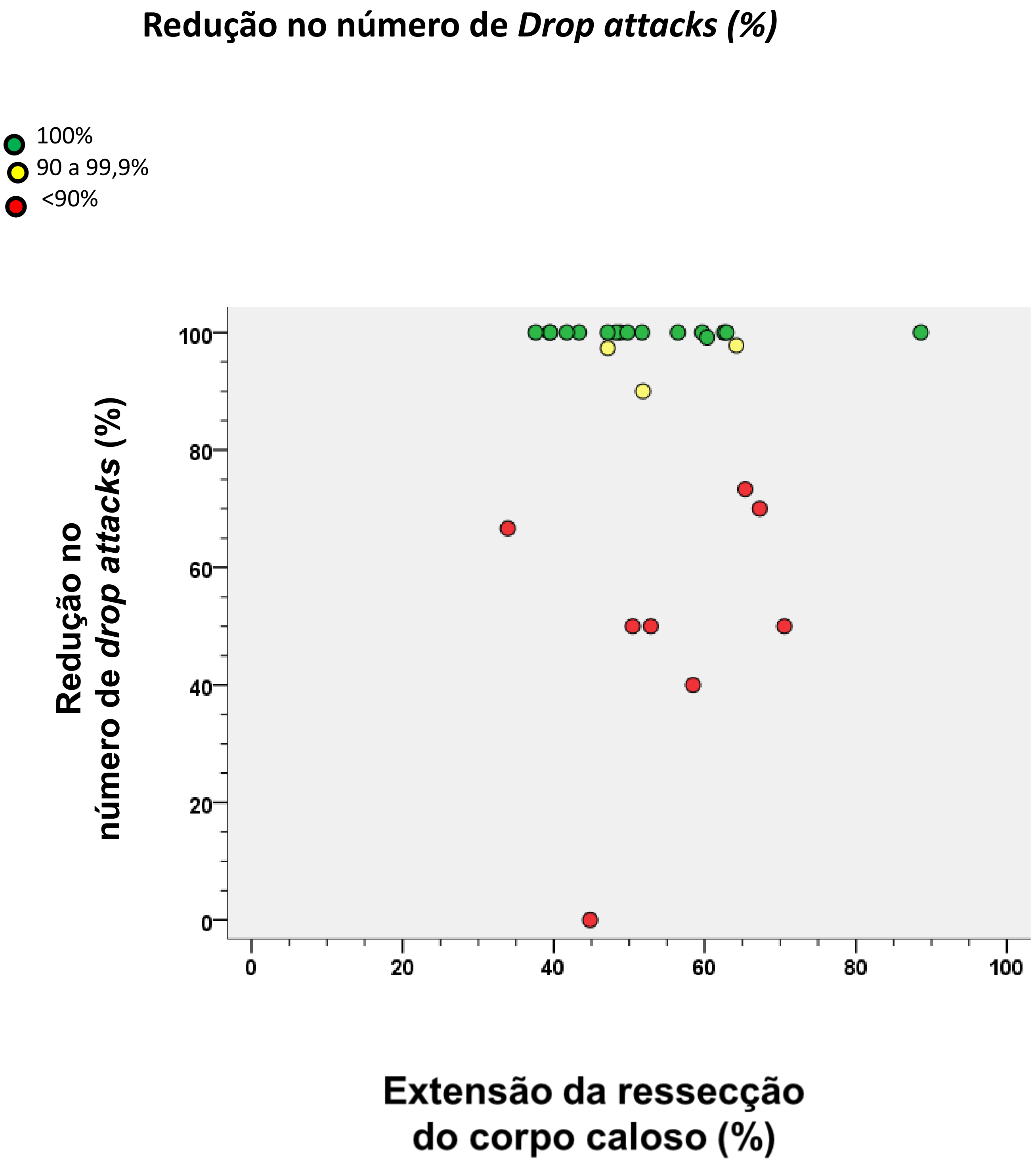


Fig 5. Correlação do índice de ressecção do corpo caloso com a redução no número de drop attacks no pós operatório de 27 pacientes. *Uma ressecção posterior mais ampla não foi sinônimo de melhor controle, entretanto, mesmo nos pacientes com uma ressecção menor, as áreas motoras primárias e as áreas motoras suplementares caudais (AMS-proper), foram desconectadas como de acordo com os achados das tractografias pós operatórias.*

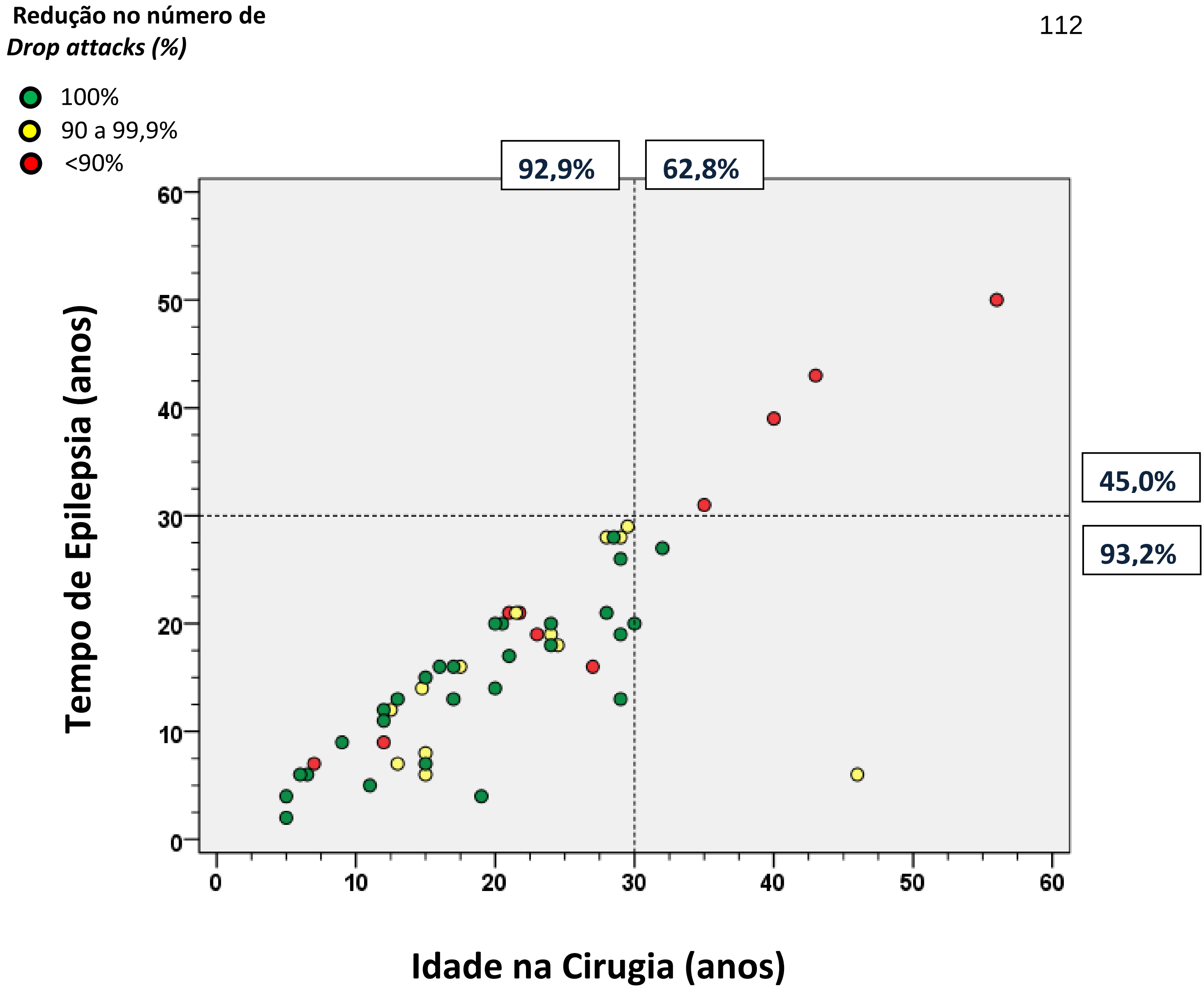


Fig 6. Correlação da redução no número de drop attacks com as variáveis idade na cirurgia e tempo de epilepsia. *Uma idade mais avançada e um tempo de doença mais longo está correlacionado com um pior controle nas crises de queda. As porcentagens na margens direita e superior do gráfico informam as melhoras em cada grupo.*

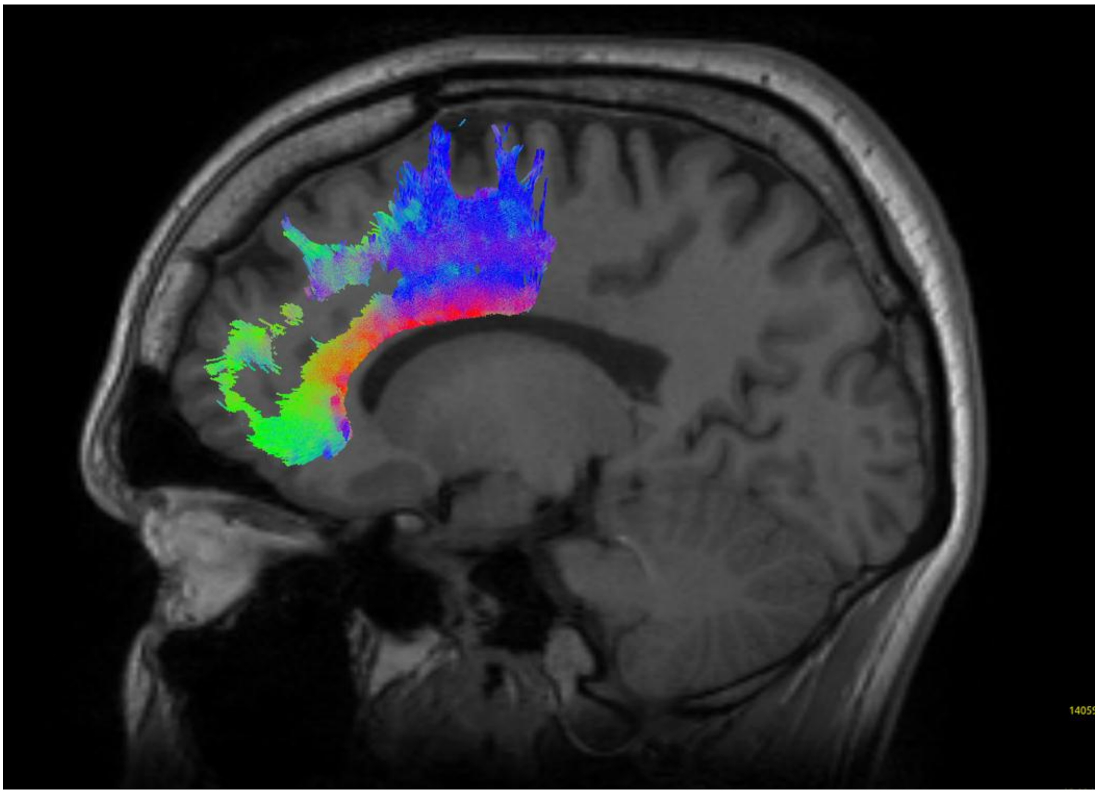


Fig. 7 RNM com tractografia de paciente com 100% de controle das crises de drop attack mostrando fibras residuais na área motora sumplementar rostral, área pré motora e pré frontal. *Área motora primária e área motora suplementar caudal sem fibras remanescentes no pós operatório.*

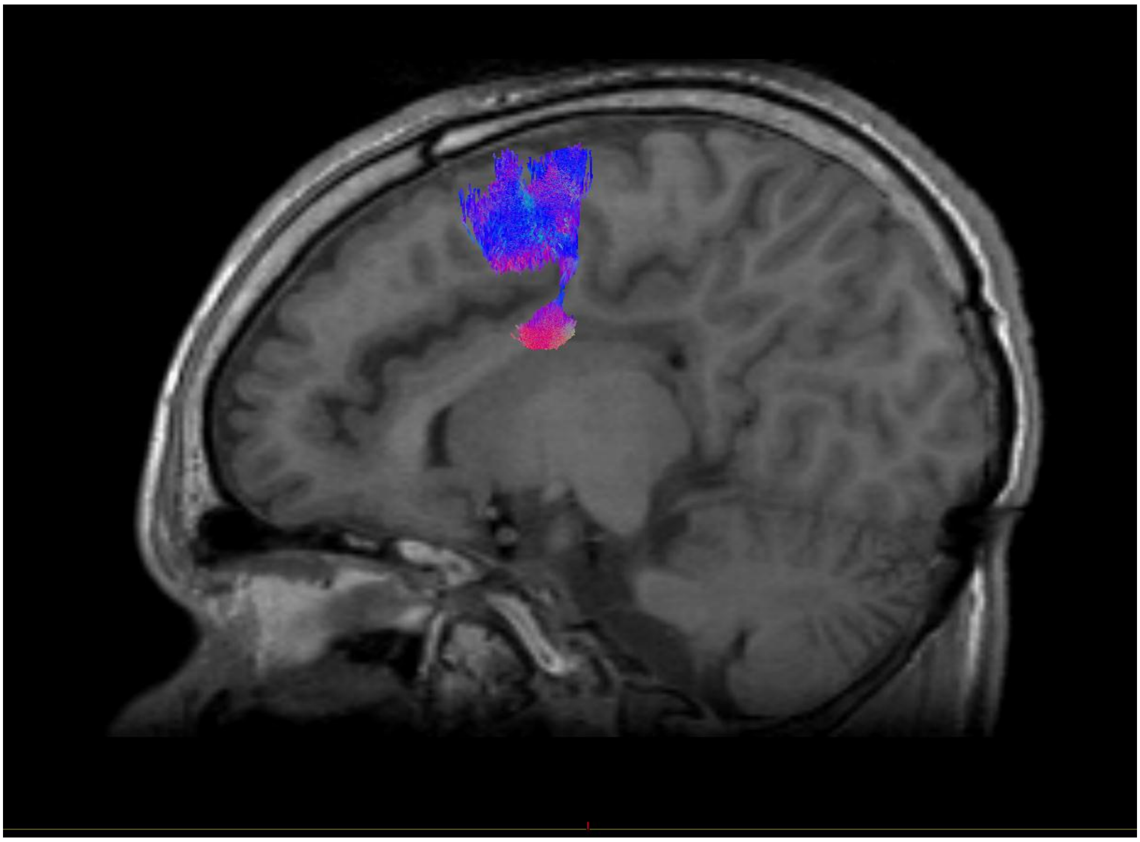
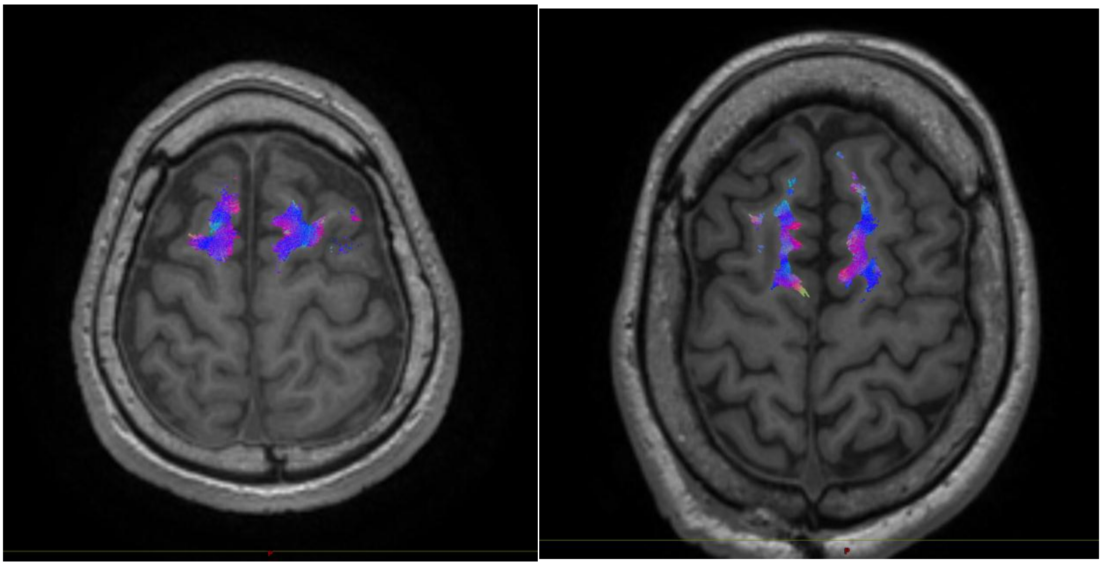


Fig. 8 RNM com tractografia de paciente sem controle das crises de drop attack mostrando fibras residuais na área motora sumplementar rostral e área pré motora. *Área motora primária e área motora suplementar caudal sem fibras remanescentes no pós operatório.*



A B

Fig 9. Comparativo entre tractografias de dois pacientes diferentes. *O primeiro (A) sem controle de drop attacks, o segundo (B), livre de drop attacks. Em ambos não há fibras residuais em área motora primária e área motora suplementar caudal. Os dois possuem fibras residuais iniciando 2cm a frente do giro motor, o que não influenciou no controle das crises.*

PATIENT	DA control	RESIDUAL CALOSAL FIBERS - DTI		
		SMAr	SMAp	M1
B.A.	100%	Yes	No	No
M.J.A.	100%	Yes	No	No
C.S.	100%	No	No	No
C.F.D.	100%	No	No	No
C.S.O.	100%	No	No	No
A.P.M.J.	100%	Yes	No	No
J.L.S.J.	100%	No	No	No
E.D.S.	100%	Yes	No	No
N.L.S.	100%	Yes	No	No
L.V.E.	100%	Yes	No	No
T.J.L.	100%	Yes	No	No
L.S.A.	100%	Yes	No	No
T.M.	90-99%	Yes	No	No
G.M.	90-99%	No	No	No
J.F.S.	<90%	No	No	No
D.S.	<90%	Yes	No	No
J.T.	<90%	No	No	No
M.C.S.	<90%	No	No	No

Tabela 1. Dados de 18 pacientes que realizaram tractografia descrevendo a redução nos drop attacks e a presença ou não de fibras residuais conectando as áreas motoras primárias, motoras suplementares caudais e motoras suplementares rostrais. *Onde: AMSp (área motora suplementar caudal), AMSr (área motora suplementar rostral), M1 (área motora primária).*

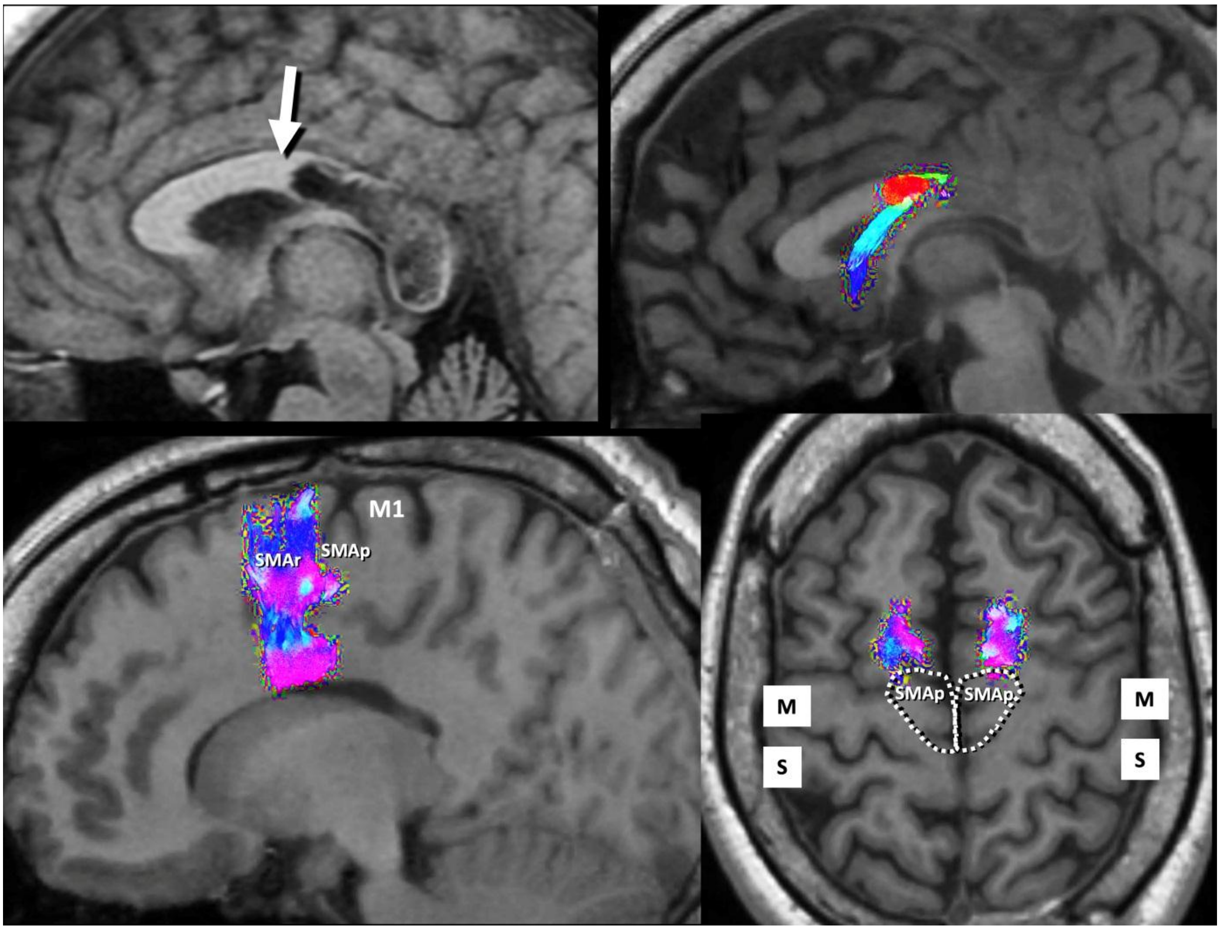


Fig 10. ROI (regions of interest) de 1cm colocado na porção distal do caloso remanescente com a finalidade de estudar a topografia das fibras calosas. As fibras que interconectam as areas motora primária (M1), e motora suplementar caudal (SMAp), estão desconectadas, enquanto as fibras interconectando as áreas motoras sumplementar rostral, pre motora e pre frontal permanecem intactas. Paciente livre de drop attacks após o procedimento.

	nome	id cir	tempo de epil	melhora (%)	Etiologia	id ini crises	crises pré	crises pós	ind_resec_caloso)%)	tam_x	tam_y
2	APM	20	20	100,00	Desconhecida	0,5	700,0	0,0	37,61	69,98	26,32
3	ASP	27	16	70,00	Lesao hipoxico-isquemica neonatal	11	300,0	90,0			
4	ACG	12	12	99,17	Lesao hipoxico-isquemica neonatal	0	60,0	0,5	60,30	52,65	31,75
5	APC	9	9	100,00	Desconhecida	0,7	12,0	0,0			
6	BZA	17	13	100,00	Desconhecida	4	50,0	0,0	39,48	66,31	26,18
7	CS	30	20	100,00	Polimicrogiria perisilviana bilateral	10	20,0	0,0	39,52	70,32	27,79
8	CTD	28	28	100,00	Prematuridade	0	90,0	0,0			
9	CF	11	5	100,00	Desconhecida	6	1500,0	0,0			
10	CG	43	43	20,00	Lesao hipoxico-isquemica neonatal	0	150,0	120,0			
11	CFD	29	19	100,00	Desconhecida	10	60,0	0,0	88,62	67,9	60,17
12	CSO	15	15	100,00	Esclerose tuberosa	0,7	300,0	0,0	59,67	69,77	41,63
13	DFS	7	7	0,00	Encefalite	0	150,0	150,0	44,82	60,87	27,28
14	ELM	15	8	98,67	Desconhecida	7	150,0	2,0			
15	EJB	24	20	100,00	Polimicrogiria perisilviana bilateral	4	300,0	0,0	48,82	77,78	37,97
16	EBS	12	12	100,00	Desconhecida	0	180,0	0,0			
17	ET	5	2	100,00	Desconhecida	3	300,0	0,0	47,14	60,29	28,42
18	FLA	24	19	96,67	Desconhecida	5	30,0	1,0			
19	FPS	12	11	100,00	Paquigiria	1	300,0	0,0			
20	GLM	28	28	97,78	TCE	0	90,0	2,0	64,19	65,84	42,26
21	GMS	32	27	100,00	Desconhecida	5	150,0	0,0			
22	GL	29	26	100,00	Desconhecida	3	8,0	0,0	62,88	69,48	43,69
23	GBM	40	39	40,00	Lesão isquêmica peri natal	1	5,0	3,0	58,44	72,24	42,22
24	HFR	12	9	66,67	Encefalopatia pós-radioterapia	3	180,0	60,0	33,92	69,99	23,74
25	HMS	24	18	99,72	Lesao hipoxico-isquemica neonatal	6	180,0	0,5			
26	IFR	13	13	100,00	Lesao hipoxico-isquemica neonatal	0	90,0	0,0			
27	JFS	23	19	50,00	Heterotopia periventricular bilateral	4	12,0	6,0	52,87	56,48	29,86
28	JT	35	31	70,00	Desconhecida	4	40,0	12,0	67,27	66,69	44,86
29	JLS	20	20	100,00	Lesao hipoxico-isquemica neonatal	0	120,0	0,0	48,25	73,79	35,6
30	JAPV	19	4	100,00	Lesao hipoxico-isquemica neonatal	15	480,0	0,0			
31	KVP	21	21	50,00	Lesao hipoxico-isquemica neonatal	0	300,0	150,0	70,53	64,31	45,36
32	LVE	6	6	100,00	Desconhecida	0	3000,0	0,0	49,77	65,18	32,44
33	LVBA	28	21	100,00	Lesao hipoxico-isquemica neonatal	7	210,0	0,0			
34	LPS	15	14	93,33	Paquigiria	1	60,0	4,0			
35	LCDG	21	21	99,64	Desconhecida	0	140,0	0,5			
36	LSA	16	16	100,00	Heterotopia periventricular	0,3	60,0	0,0	56,43	72,07	40,67
37	MPE	29	13	100,00	Desconhecida	16	120,0	60,0	50,45	60,85	30,7
38	MGB	56	50	50,00	Lesao hipoxico-isquemica neonatal	6	5,0	0,0	43,36	68,27	29,6
39	MJP	20	14	100,00	Desconhecida	6	120,0	0,0	62,55	80,46	50,33
40	MMN	30	29	99,44	Paquigiria	1	90,0	0,5			
41	MCS	21	21	73,33	Desconhecida	0	120,0	32,0	65,35	70,91	46,34
42	NLS	6	6	100,00	Desconhecida	0,5	2000,0	0,0	41,73	66,04	27,56
43	PMPL	17	16	98,33	Desconhecida	1	60,0	1,0			
44	RA	13	7	99,58	Desconhecida	6	120,0	0,5			
45	RRM	15	7	100,00	Desconhecida	8	60,0	0,0			
46	RNR	46	6	97,33	Prematuridade	40	450,0	12,0	47,15	72,53	34,2
47	TM	15	6	90,00	Lesao hipoxico-isquemica neonatal	9	1200,0	120,0	51,81	71,49	37,04
48	TRB	17	16	100,00	Desconhecida	1	180,0	0,0			
49	TJL	24	18	100,00	Desconhecida	6	100,0	0,0	51,70	76,08	39,33
50	VHR	5	4	100,00	Desconhecida	1	600,0	0,0			
51	WH	21	17	100,00	Polimicrogiria perisilviana bilateral	4	24,0	0,0			
52	XT	29	28	99,33	Lesao hipoxico-isquemica neonatal	1	150,0	1,0			

Tabela 2. Dados demográficos e resultados cirúrgicos dos 51 pacientes do estudo onde: ic cir (idade na cirurgia); tempo de epil (tempo de epilepsia na cirurgia); id ini crises (idade de início das crises); crises pré (crises de queda/mês no pré op); crises pós (crises de queda/mês no pós op); tam_x (tamanho total do caloso); tam_y (tamanho da porção posterior do caloso ressecada na cirurgia); ind_resec_caloso (porcentagem do caloso ressecado).

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