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Control of drop attacks with selective posterior callosotomy: Anatomical and prognostic data☆

Thomas Frigeri [a,*], Eliseu Paglioli [a,c], Ricardo Bernardi Soder [a,b,c], William Alves Martins [a], Rafael Paglioli [a], Rita Mattiello [c], Ricardo Paganin [a,b], André Palmini [a,c,*]

[a] Porto Alegre Epilepsy Surgery Program, Neurology and Neurosurgery Services, Hospital São Lucas, Brazil
[b] The Brain Institute, Brazil
[c] School of Medicine, Pontificia Universidade Catolica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

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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: Mean monthly frequency of drop attacks had a 95 % reduction, from 297 before to 16 after the procedure. Forty- one patients (80 %) 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 areas (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 half of the body (posterior midbody) seems sufficient to achieve complete or almost complete control of drop attacks.

1. 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 both 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 (Van Wagenen and Herren, 1940; Shim et al., 2008; Stigsdotter-Broman et al., 2014; Pinard et al., 1999a).

In most centers, corpus callosotomy is performed by sectioning variable extents of the so-called anterior callosum (ie, from the rostrum, through the genu to the anterior midbody), and often transformed into a more efficacious total disconnection when patients fail the initial procedure (Spencer, 1988; Spencer et al., 1988; Reutens et al., 1993; Chan et al., 2018; Jea et al., 2008; Asadi-Pooya et al., 2008; Maehara and Shimizu, 2001). 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 premotor and primary motor cortices cross in the anterior half of the CC (Witelson, 1989). Recently, however, modern imaging and brain dissection techniques have challenged this anatomical view, showing that callosal fibers

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* Corresponding authors at: Service of Neurology, Hospital São Lucas da PUCRS, Avenida Ipiranga 6690, CEP: 90610-000, Porto Alegre, RS, Brazil.
E-mail addresses: tfrigeri@terra.com.br (T. Frigeri), andre.palmini@pucrs.br (A. Palmini).

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originating in primary motor cortex cross more posteriorly, between the body and the splenium (Zarei et al., 2006; Aboitiz et al., 1992; Fabri et al., 2011; Park et al., 2008).

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 postulated 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 (Paglioli et al., 2016).

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 (Chan et al., 2018). Similar data regarding selective posterior callosotomy is nonexistent.

Here we report an extension of the follow up of the original 36 and add 15 new consecutive patients, thus increasing the sample to 51 patients with disabling drop attacks who had selective posterior callosotomy. Demographic and imaging variables were correlated with degree of control of falls. Moreover, we refined the imaging analyses in half the sample using MRI and tractography (DTI) to study the extent of callosal section. 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.

2. 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 (Paglioli et al., 2016). 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 bisynchronous 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 lissencephaly, 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. Variations in age, etiology or baseline frequency of falls were not exclusion criteria. All operated patients were deemed in good clinical condition to undergo the procedure. 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 1.5 T Siemens machine (Siemens AG, Erlangen, Germany) whereas in patients 37–51 (Table 1) in a 3.0 T 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 developed and index to calculate the extent of the CC section. First, we measured the distance between the anteriormost portion of the CC, ie the anterior limit of the genu, (rostral and anterior to the rostrum) to the posterior limit of the splenium (variable X). Then, we measured the sectioned portion of the CC from the anterior to the posterior margin of the section, ie, the posterior limit of the splenium (variable Y). This ratio (Y / X), is illustrated in Fig. 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 (Andersson and Sotiropoulos, 2016) and fiber orientation distribution maps were generated with the MRTrix spherical deconvolution algorithm (Tournier et al., 2007) using factor of 6 as maximum harmonic order. Tracts generation for each patient were 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 (Tournier et al., 2010) (iFOD2). 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 1 cm 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.

Table 1
Demographic data.

Patient	Age at Surgery	Epilepsy Duration	Etiology	Pre-op DA*	Post-op DA*	% Reduction	Callosal section index %
1	20	20	Unknown	700	0	100	38
2	27	16	Hypoxic ischemic perinatal lesions	300	90	70	N/A
3	12	12	Hypoxic ischemic perinatal lesions	60	0.5	99	60
4	9	9	Unknown	12	0	100	N/A
5	17	13	Unknown	50	0	100	39
6	30	20	Bilateral perisylvian polymicrogyria	20	0	100	40
7	28	28	Prematurity	90	0	100	N/A
8	11	5	Unknown	1500	0	100	N/A
9	43	43	Hypoxic ischemic perinatal lesions	150	120	20	N/A
10	29	19	Unknown	60	0	100	89
11	15	15	Tuberous Sclerosis	300	0	100	60
12	7	7	Encephalitis	150	150	0	45
13	15	8	Unknown	150	2	99	N/A
14	24	20	Bilateral perisylvian polymicrogyria	300	0	100	49
15	12	12	Unknown	180	0	100	N/A
16	5	2	Unknown	300	0	100	47
17	24	19	Unknown	30	1	97	N/A
18	12	11	Lyssencephaly	300	0	100	N/A
19	28	28	Trauma	90	2	98	64
20	32	27	Unknown	150	0	100	N/A
21	29	26	Unknown	8	0	100	63
22	40	39	Hypoxic ischemic perinatal lesions	5	3	40	58
23	12	9	Encephalopaty due to radiotherapy	180	60	67	34
24	24	18	Hypoxic ischemic perinatal lesions	180	0.5	99	N/A
25	13	13	Hypoxic ischemic perinatal lesions	90	0	100	N/A
26	23	19	Bilateral periventricular heterotopia	12	6	50	52
27	35	31	Unknown	40	12	70	67
28	20	20	Hypoxic ischemic perinatal lesions	120	0	100	48
29	19	4	Hypoxic ischemic perinatal lesions	480	0	100	N/A
30	21	21	Hypoxic ischemic perinatal lesions	300	150	50	71
31	6	6	Unknown	3000	0	100	50
32	28	21	Hypoxic ischemic perinatal lesions	210	0	100	N/A
33	15	14	Lyssencephaly	60	4	93	N/A
34	21	21	Unknown	140	0.5	99	N/A
35	16	16	Unilateral periventricular heterotopia	60	0	100	56
36	29	13	Unknown	120	60	100	50
37	56	50	Hypoxic ischemic perinatal lesions	5	0	50	43
38	20	14	Unknown	120	0	100	63
39	30	29	Lyssencephaly	90	0.5	99	N/A
40	21	21	Unknown	120	32	73	65
41	6	6	Unknown	2000	0	100	42
42	17	16	Unknown	60	1	98	N/A
43	13	7	Unknown	120	0.5	99	N/A
44	15	7	Unknown	60	0	100	N/A
45	46	6	Prematurity	450	12	97	47
46	15	6	Hypoxic ischemic perinatal lesions	1200	120	90	52
47	17	16	Unknown	180	0	100	N/A
48	24	18	Unknown	100	0	100	52
49	5	4	Unknown	600	0	100	N/A
50	21	17	Bilateral perisylvian polymicrogyria	24	0	100	N/A
51	29	28	Hypoxic ischemic perinatal lesions	150	1	99	N/A

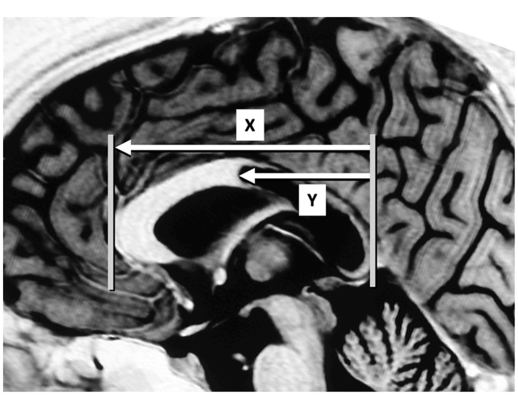

Fig. 1. Y/X: extent of posterior section of the corpus callosum as a ratio of the sectioned area (Y) and the entire callosal extension (X).

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. Before decision on surgical candidacy, patients were all tried on combination of valproate, lamotrigine, and a benzodiazepine as this regimen has proved effective in reducing the frequency of drop attacks in many patients (Machado et al., 2011). Operations were performed following at least one year of observation and dose adjustments of this 'trio', when it became clear to neurologists and families that a satisfactory control of drop attacks could not be achieved with medication only. Likewise, all were stabilized on this same combination of anti-seizure medications after operation. Doses were allowed to change over the years, according to occasional relapses or side effects.

Patients were classified in 3 groups: free from drop attacks (i), reduction $\geq$ 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.

2.1. 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 tested several cutoffs and, eventually, subdivided age at surgery and duration of epilepsy in 0–30 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 frequencies of drop attacks wer 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 one-way 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.

3. Results

3.1. Control of drop attacks

Median and mean monthly frequencies of drop attacks before surgery were respectively 120 (Interquartile range - IQR: 240) and 297 (min 5 - max 3000; 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 (803%) had complete remission or a higher than 90 % reduction in the frequency of drop attacks, and only 10 patients (197 %) 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.

3.2. Demographic and clinical variables related to surgical outcome

Forty-five patients were younger than 30 years and 6 were older. After testing for distinct cut-offs, despite the relatively small figures significance was observed when contrasting patients who were younger or older than 30 years at surgery in relation to degree of 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.

3.3. 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 Fig. 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 SMA and PMA 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:

3.4. Age at surgery x Duration of epilepsy x Reduction of drop attacks -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 Fig. 4.

3.5. 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 h 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

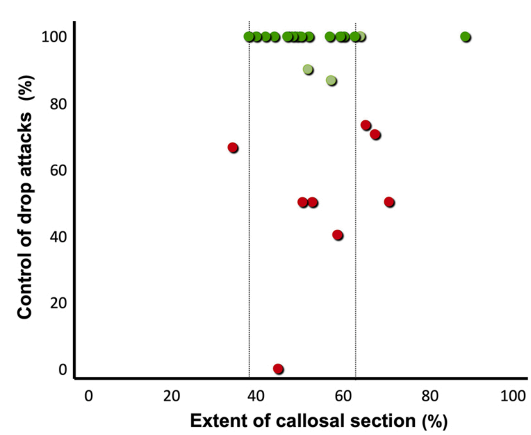

Fig. 2. Lack of significant relationship between index of callosal section and rate of control of drop attacks. Note that some patients had excellent outcome and smaller sections, whereas others had extended sections but did not do as well (Table 1).

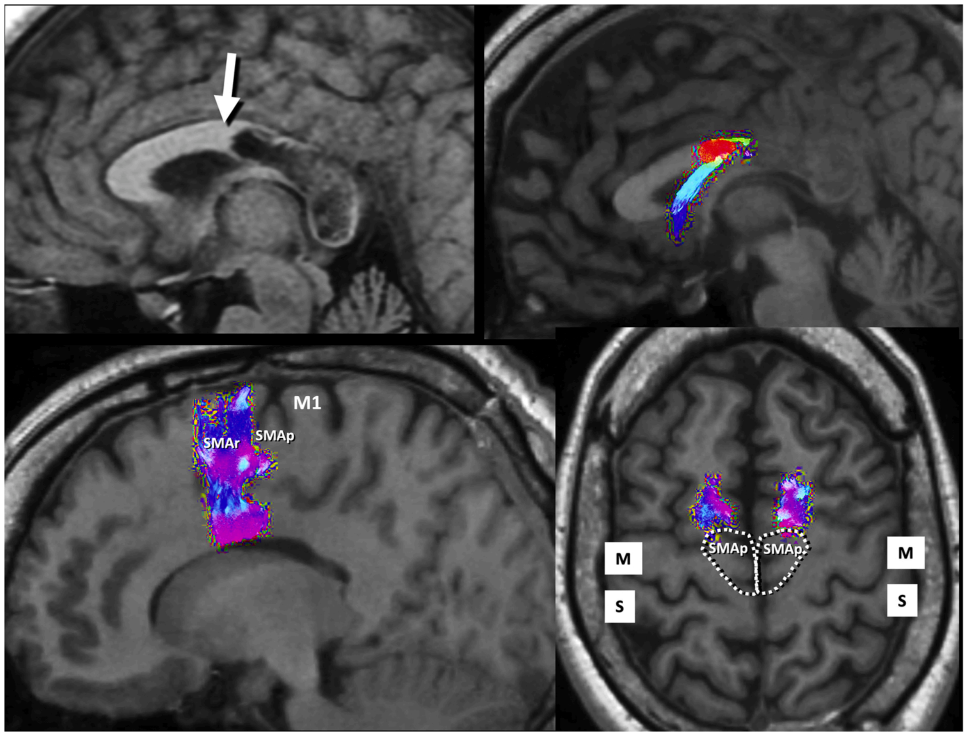

Fig. 3. Post operative tractography in a patient who had selective posterior callosotomy. ROI was placed at the distal remaining CC. Fibers interconnecting homologous M1 (primary motor area), S1 (primary sensory area) and the caudal SMA (SMA proper – SMAp) are absent while present in rostral SMA (SMA rostral – SMAr). Patient is free of drop attacks.

had a small intracranial hematoma at the surgical site, with no intracranial hypertension. He was somnolent for 2 days and recovered completely with conservative treatment.

4. 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 possibly sparing prefrontal interconnectivity (callosal section stopped at the midbody in all patients and the anterior half of the corpus callosum was left intact) 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 (Paglioli et al., 2016). 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.

We hypothesized that significant control of atonic and tonic seizures needed sectioning the callosal fibers originating from M1 and the premotor area (PMA), including those associated with negative motor phenomena (Zarei et al., 2006; Paglioli et al., 2016; Witelson, 1989; Oguni et al., 2001; Maillard et al., 2014; Lüders et al., 1995). 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. The lack of correlation between the extent of callosal section in the posterior-to-anterior axis with seizure control is most likely due to individual variation of the exact point of crossing of motor fibers along the midbody. Hence, the combination of our data and experience strongly suggest that at least 40 % of the corpus callosum in the posterior-to-anterior axis should be disconnected, always including the splenium, the isthmus and the posterior portion of the body.

Although the traditional and most used approach, anterior corpus callosotomy usually achieves complete control of drop attacks in a small percentage of patients. For instance, in the Mayo clinic series (Bower et al., 2013) only 8 of 33 patients (24 %) in whom only the anterior two-thirds of the callosum was sectioned had complete control of falls. Other series of anterior callosal sections reported rates of reduction of 75–100 % of falls in only 25–70 % of patients (Tanriverdi et al., 2009; Chan et al., 2018; Graham et al., 2018). Thus, many patients are often considered for a second procedure, transforming an anterior in a total callosotomy. In fact, the literature leaves little doubt that larger callosal sections are associated with better control of atonic seizures (Sunaga et al., 2009; Reutens et al., 1993; Chan et al., 2018; Gazzaniga et al., 1975; Maehara and Shimizu, 2001). 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 (Spencer et al., 1993), and in children after West syndrome, total section controlled falls in 89 % compared to 27 % when only the anterior callosum was sectioned (Pinard et al., 1999b). 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 (Chan et al., 2018). These contrasting results led to the contention that total callosotomy would be the most effective strategy to control epileptic falls. Interestingly, complete or greater than 90 % control of drop attacks was achieved by 80 % of patients having selective posterior callosotomy in this extended series, similar to the 83 % reported in the original series. This is a comparable performance to total callosotomies (Tanriverdi et al., 2009; Sunaga et al., 2009; Paglioli et al., 2016; Chan et al., 2018; Gazzaniga et al., 1975) and hence strongly suggests that preservation of the anterior callosal fibers interconnecting prefrontal regions is not relevant to surgical outcome. Such results led us to hypothesize in our previous study 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 (Palmini and Paglioli, 2018). That hypothesis

Table 2
Individual tractography data with anatomical specificity in motor regions: Residual fibers interconnecting homologous motor regions (M1, caudal and rostral SMA).

PATIENT	DA control	RESIDUAL CALLOSAL FIBERS - DTI		
		SMA rostral	SMA caudal	M1
1	100 %	Yes	No	No
2	100 %	Yes	No	No
3	100 %	No	No	No
4	100 %	No	No	No
5	100 %	No	No	No
6	100 %	Yes	No	No
7	100 %	No	No	No
8	100 %	Yes	No	No
9	100 %	Yes	No	No
10	100 %	Yes	No	No
11	100 %	Yes	No	No
12	100 %	Yes	No	No
13	90–99 %	Yes	No	No
14	90–99 %	No	No	No
15	<90 %	No	No	No
16	<90 %	Yes	No	No
17	<90 %	No	No	No
18	<90 %	No	No	No

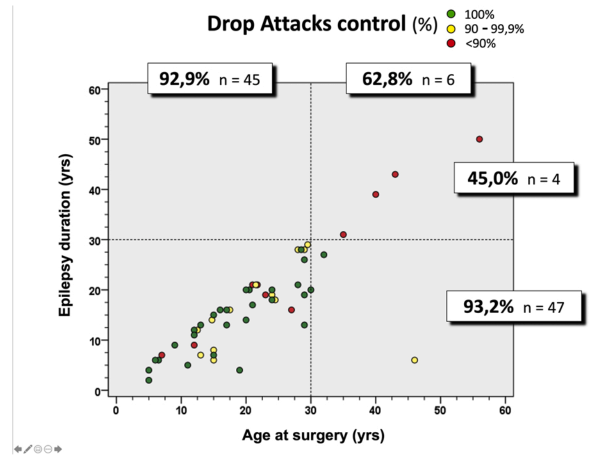

Fig. 4. Graphic illustration of the multivariate relationship between age at surgery and duration of epilepsy with rate of control of drop attacks as dependent variable. Note that patients in the right upper quadrant – with longer duration and older age at operation - had the worst results.

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 (Paglioli et al., 2016) 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 (Zarei et al., 2006; Hofer and Frahm, 2006; Park et al., 2008). Because bilateral epileptic synchronization of these motor regions is thought to lead to sudden, generalized atonic and tonic seizures through a fast-conducting polysynaptic mechanism involving the brainstem and spinal cord (Andersson and Sotiropoulos, 2016), 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 (Aboitiz et al., 1992).

Although not examined in this extended series, selective posterior callosotomy was shown to improve functionality in patients with severe encephalopathies and sudden falls (Paglioli et al., 2016), 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 (Chan et al., 2018), 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 (Gazzaniga et al., 1975; Gazzaniga, 2015; Lassonde et al., 1995).

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 (Maehara and Shimizu, 2001), and that adults had significantly higher risk of complications (Gazzaniga et al., 1975; Lassonde et al., 1995). Because most patients in this and other series have exceedingly frequent generalized 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 (Jeha et al., 2007; Meguins et al., 2015). 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 analyzed, 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 (Aboitiz et al., 1992). 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 (Zilles et al., 1996; Schwartze et al., 2012). 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 (Asadi-Pooya et al., 2008). 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 (Rhoton, 2007; Frigeri et al., 2015).

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.

We did not analyse the relation of preoperative EEG abnormalities on the control of drop attacks nor the impact of surgery on patients' cognition and functionality. These issues 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 (Paglioli et al., 2016). 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 (Rolston et al., 2015). 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 analyzed 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 generalizability of the findings, although it mirrors what is actually seen at busy epilepsy clinics. Another relevant limitation is that we limited the analysis to a straightforward quantification of falls and did not analyzed the impact of the procedure on the frequency of generalized tonic-clonic seizures. This is an important, practical outcome, not addressed here. Furthermore, we failed to explore the issue of the damage of hypoxic ischemic perinatal lesions on callosal fibers, and how this could have impacted our findings. Hypoxic ischemic lesions were a prevalent etiology in our series and we left a number of questions unanswered, such as whether the post-op tractography in the hypoxic ischemic group related to the pre-operative degree of injury and also whether patients with perinatal hypoxic ischemic lesions already had a thinned corpus callosum and damaged transcallosal motor tracts. Finally, due to the lack of availability of genetic testing, we were not able to distinguish a truly unknown etiology from a genetic developmental and epileptic encephalopathy in patients in whom MRI was normal.

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 (Sidtis et al., 1981).

Author's contribution

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. TF, AP and EP designed the study, coordinated data collection and wrote the first draft of the manuscript. TF, WM and RP obtained demographic data and RBS and TF obtained and interpreted imaging data, and wrote parts of the manuscript. RM and TF performed the statistical analyses.

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Appendix A. Supplementary data

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