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Effective posterior extension of callosotomy by gamma knife surgery

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ABSTRACT – Drop attacks are the most responsive seizure type to open callosotomy, however, surgical complications can worsen the prognosis. Various less invasive techniques have been explored in an effort to minimize the risk. We present a patient who suffered from life-threatening traumatizing drop attacks in whom previous open anterior callosotomy and vagal nerve stimulation were unsatisfactory. Following posterior extension of the callosotomy by non-invasive gamma knife surgery, the rate of drop attacks declined from 30 a day to once a day, or every few days over a four-month period, without complications.

Open callosotomy is an invasive and high risk treatment option for patients with drop attacks. The procedure has a potential for complications and neurological consequences that can worsen the functional capacity of a patient who already suffers with disability. Recently, in an attempt to decrease the invasiveness associated with this technique, additional technical refinements and less invasive procedures have been explored in a few studies. Here, we report a case of refractory epilepsy with life-threatening traumatizing DA, in which the patient was treated by radiosurgical posterior callosotomy after unsatisfactory open anterior callosotomy and vagal nerve stimulation.

Key words: epilepsy, drop attacks, callosotomy, step-wise, gamma knife, radiosurgery, minimally invasive

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Case study

History and clinical and neuroimaging findings

A 26-year-old woman presented with chronic resistant epilepsy which started with infantile spasms. She presented with multiple seizure types, including tonic seizures, complex partial seizures, secondary generalized tonic-clonic seizures (GTCS) and DA. The seizure frequency was 30 attacks per day with recurrent facial trauma, wounds, haematoma and broken teeth. DA was the main dominating presentation accompanied by other seizure types. Delayed psychomotor development and poor school performance were associated with some autistic behaviour. Secondary amenorrhea, hypertrichosis and gingival hypertrophy were associated with global developmental delay. Reflexes were normal with no neurological deficit. Karyotype and metabolic assessment were completely normal. Brain magnetic resonance imaging (MRI) revealed left insular abnormal thickening, consistent with focal cortical dysplasia, as well as the previous open anterior callosotomy. Positron-emission tomography (PET) showed diffuse hypometabolism on bilateral frontal and temporal regions, particularly on the left insula and temporo-occipital junction.

Previous intervention

Vagal nerve stimulation and open anterior callosotomy were attempted when the patient was 14 and 21 years of age, respectively, with unsatisfactory results. Worsening of EEG and clinical aspects continued postoperatively.

Video scalp EEG

EEG showed a multifocal pattern and abundant interictal activity mainly in the left temporo-frontal region (slow waves and spikes) with paroxysmal activity, which predominated in the left frontal region. Numerous tonic seizures were recorded with elevation and flexion of both upper limbs as well as falls, sometimes triggered by noise, with significant contralateral involvement.

Surgical technique

Following a multidisciplinary discussion, the decision was made to extend the callosotomy by gamma knife surgery. A Leksell frame was applied under local anaesthesia. Brain MRI was performed using a Siemens Magnetom Aera 1.5 T MRI machine (Siemens, Erlangen, Germany). Images were obtained using thin slices (1 mm) in Turbo Spin sequence (TSE), coronal T2-weighted fast spin-echo, T1-weighted 3D MRI with gadolinium (MPRAGE) and constructive interference in steady state (CISS).

Preoperative tractography was co-registered with the stereotactic images. Gamma knife callosotomy (GK-C) for the posterior third of the callosotomy was performed using the planning system of Leksell Gamma Plan version 10.1.1 and Leksell Gamma Knife PerfeXion (Elekta Instrument AB, Stockholm, Sweden).

The marginal dose used was 60 Gy for 50% perception isodose line (*figure 1*). The treated volume of corpus callosum was 1.36 cm^3. During the whole procedure, the patient was closely monitored. She was discharged the day after the intervention.

Results and follow-up

The patient began to improve two months after GK-C. We observed a marked reduction in the frequency of drop attacks from 30 per day to once a day, or every few days over a period of four months. Mild infrequent residual partial seizures persisted. We followed the patient for 33 months without change in antiepileptic medication. Subsequently, the patient subjectively reported significant improvement in sleep quality, cognitive function and behavioural aspects. Neither surgical complications nor neurological consequences were observed. We observed mild transient headache and tolerable transient oedema with clear regression under corticosteroid therapy within two months.

Average fractional anisotropy of the corpus callosum was reduced from 0.39 to 0.29, one year after GK-C, based on the Fibertracking tool of Elements software (BrainLAB, Feldkirchen, Germany), with the following parameters: min FA: 0.2; max FA: 1.0 min; fibre length: 10.0 mm.

Discussion

Open corpus callosotomy

Dr. William P. van Wagenen, cofounder and first president of the American Association of Neurological Surgeons (AANS), was the first to attempt, study, and publish results of the corpus callosotomy procedure for epilepsy in the 1940s (Van Wagenen and Herren, 1940). The results of "split-brain" features later led to Roger Sperry being awarded the 1981 Alfred Nobel Memorial Prize for Physiology and Medicine (Shampo and Kyle, 1995).

Corpus callosotomy can prevent or minimize epileptic activity between the two cerebral hemispheres. Callosotomy is associated with a better outcome over other procedures, in particular, vagal nerve stimulation which can cause hoarseness, coughing, tingling

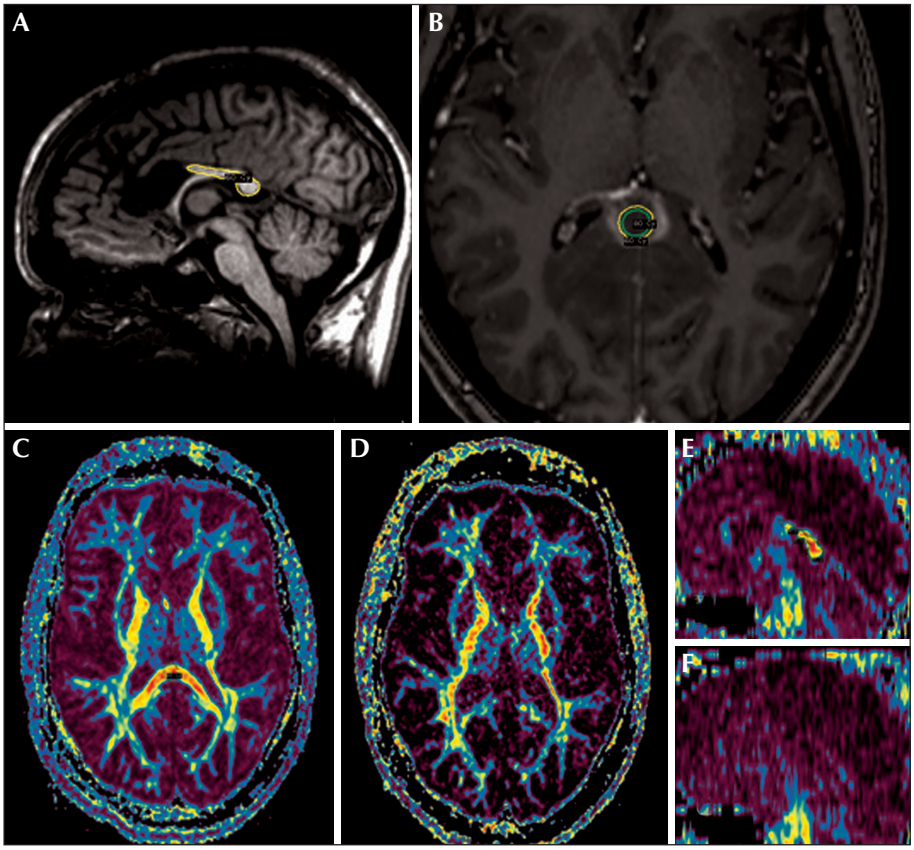

Figure 1. (A) Gamma knife posterior callosotomy with eight shots of 4-mm collimators and one shot of 8-mm collimators making it possible to deliver a dose of 60 Gy at 50% isodose at the level of the residual part of CC. The total volume of the prescription isodose was 1.36 cm^3. (B) Axial T1-weighted image with gadolinium contrast demonstrates the enhanced signals around the isodose line. C-F) Tractrography demonstrating the level of reduced corpus callosum signal relative to before GK-C (C, E) and after GK-C (D, F).

in the throat, voice alteration during stimulation, and infection (Lancman *et al*., 2013).

The reduction in frequency of DA varies between 60% and 100%. GTCS respond well (>50% reduction) in about 35% to 40% after anterior callosotomy (Graham *et al*., 2018). Recent evidence indicates that favourable electroclinical outcomes following callosotomy are associated with prolonged life expectancy compared with medicine-based management.

Numerous surgical complications associated with open callosotomy should be considered such as infection (1-12%), intracranial haematoma (1-10%), brain oedema/swelling (0-3%), stroke (0-1.5%), meningitis, mutism, hemiparesis and death (0-2.8%). Neurological consequences including disconnection syndrome (13% of cases), apraxia, tactile and/or visual anomia, agraphia, neglect, and dyslexia have been reported (Quattrini *et al*., 1997; Graham *et al*., 2016, 2018; McGonigal *et al*., 2017).

Additional techniques have been explored including an anterior frontal interhemispheric approach, staged callosotomy, anterior callosotomy, and, recently, less invasive techniques to minimise complications (McGonigal *et al*., 2017).

Less invasive callosotomy

Numerous case reports and case series of minimally invasive procedures have been reported including laser interstitial thermal therapy (LiTT) (Palma *et al*., 2019), endoscopy (Sood *et al*., 2015), and radiofrequency (Patil *et al*., 1995). These are safe, effective, and durable alternatives to the traditional open corpus callosotomy but not expected to replace it. To date, there is no comparative study or studies with large series with long-term follow-up that have truly evaluated these techniques. Each case report has its unique clinical scenario and its point of strength.

Pendl *et al*. (Pendl *et al*., 1999) was the first to introduce radiosurgical callosotomy for three patients with a maximum dose of 170 Gy without major complications, demonstrating very significant reduction in atonic seizures and GTCS frequency. Moreover, significant improvement after radiosurgical callosotomy

Table 1. Summary of radiosurgical callosotomy studies published to date.

Reference	No. of patients	Age (years)	Duration (years of epilepsy)	Extent of callosotomy	Radio-surgery	Dose (Gy)	Follow-up (months)	Patient characteristics	Outcome	Complications and negative outcome
Pendl *et al.*, 1999	3	30, 31, 70	20- 37	ACC	GK	50-85 Gy	38	LGS (2 pts) Multifocal, atonic, tonic-clonic, AB, GTCS (1 pt)	Significant improvement of seizure frequency	Transient headache (1 pt)
Feichtinger *et al.*, 2006*	8	5 to 69		ACC (6 pts) ACC, MCC (1 pt) PCC after partial hemi-spherotomy (2 pts)	GK	50-85 Gy	58	Generalized epilepsy with DA Two: post-hemispherotomy	100% reduction of DA (3 pts) 60% reduction of DA (2 pts) 100% reduction of GTCS (2 pts) 50-60% reduction of GTCS (2 pts) no effects (2 pts)	Transient headache (1 pt) Transient headache and nausea after 6 months for 4 months (1 pt)
Eder *et al.*, 2006	3	4, 6, 14	3,5,13	PCC, ACC	GK	55-60	35 (22–60)	Previous hemispherotomy and paracallostomy, hemispheric cortical dysplasia (2 pts) LGS with post-encephalitis (1 pt)	100% reduction of GTCS (2 pts) 20-70% for CP Mentally improved AEDs were not reduced	No effect (LGS, post-encephalitic) (1 pt)
Celis *et al.*, 2007	1	17	16	ACC, MCC	LINAC	The prescription dose was 36.0 Gy (40.0 Gy at the iso-center) at the periphery of the target.	32	Multifocal, partial motor, CP, atypical AB, GTCS, DA, neonatal asphyxia, brain atrophy	84% reduction of seizures Behavioural improvement	Transient headache Transient left hemiparesis

Table 1. Summary of radiosurgical callosotomy studies published to date (*continued*).

Reference	No. of patients	Age (years)	Duration (years of epilepsy)	Extent of callosotomy	Radio-surgery	Dose (Gy)	Follow-up (months)	Patient characteristics	Outcome	Complications and negative outcome
Smyth *et al.*, 2007	1	9	7	PCC after open ACC	GK	65 Gy at 50% prescription isodose line	12	LGS, failed VNS, failed open ACC, GTCS. atonic, tonic-clonic, and simple partial.	Significant improvement Behavioural improvement Reduction of AED	No
Bodaghabadi *et al.*, 2011	1	13	3	ACC, MCC	GK	A maximum dose of 50.51 Gy, with a marginal dose of 22.2 Gy on 99% perception isodose	20	Generalized, complex partial. tonic, clonic, tonic-clonic and AB	Seizure-free Behavioural improvement Stop AED	No

Pt: patient; LGS: Lennox-Gastaut syndrome; CP: complex partial; AB: absence; GTCS: generalized tonic-clonic seizure; DA: drop attacks; VNS: vagal nerve stimulation; ACC: anterior corpus callosotomy; MCC: middle corpus callosotomy; PCC: posterior corpus callosotomy; VNS: vagal nerve stimulation.
**The study of Feichtinger et al. (2006) included those reported by Pendl et al. (1999).

regarding disabling seizures, particularly DA and GTCS, has been described across all published studies without serious adverse effects, in comparison to the traditional open technique (*table 1*) (Eder *et al*., 2006; Feichtinger *et al*., 2006; Celis *et al*., 2007; Smyth *et al*., 2007; Bodaghabadi *et al*., 2011). As in our case report, there were no neurological consequences or surgical complications except for mild tolerable oedema, which resolved with short-term corticosteroid therapy.

Extent of callosotomy

The techniques and extent of callosotomy vary across surgical centres. The rationale for anterior callosotomy sparing the splenium is to preserve sufficient fibres in order to diminish the risk of neurological consequences (Abou-Khalil, 2010), particularly disconnection syndrome. However, patients with unsuccessful open two-third anterior callosotomy who subsequently underwent a second surgery for complete callosotomy, and those who underwent upfront complete callosotomy, experienced improvement for a broader spectrum of seizure types than those who underwent only a two-third anterior callosotomy (Smyth *et al*., 2007). The topological orientation and representation of frontal and temporal fibres in posterior corpus callosum can explain the unsatisfactory outcome of anterior callosotomy (Hofer and Frahm, 2006). However, there is a risk of seizure recurrence even after complete callosotomy (Sunaga *et al*., 2009).

The potential for postoperative complications should be carefully considered when deciding on the extent of disconnection (Smyth *et al*., 2007). Kim *et al*. described seizure-free outcome after open posterior extension of callosotomy with disconnection syndrome (19%), aphasia, hypotonia, osteomylitis and aseptic meningitis (5%) (Kim *et al*., 2004). Others reported effective and safe posterior extension of callosotomy using less invasive techniques such as robotic LiTT (Singh *et al*., 2017).

The decision to perform corpus callosotomy is made frequently for functionally impaired patients, and any surgery-associated complication can undermine functional recovery (Singh *et al*., 2017). Venous complications, an interhemispheric route, and damage to the callosomarginal and pericallosal arteries can lead to ischaemia. Retraction injury to the cingulate gyrus and paracentral lobule can be associated with cognitive and motor complications, respectively (Schaller and Cabrilo, 2015; Singh *et al*., 2017).

Radiosurgical dose and effect

The radiosurgical dose varies between 55 and 85 Gy as a marginal dose (the highest maximum dose reported is 170 Gy). There is a much higher dose-volume ratio for radiosurgical corpus callosotomy than radiosurgical treatment of mesial temporal epilepsy. This high dose within a relatively small volume produces focal fibre destruction (Moreno-Jiménez *et al*., 2012).

We reported a favourable outcome with 98% reduction in seizure frequency within a relatively short postoperative time (2-4 months). Celis *et al*. and Eder *et al*. reported reduction by 84% within 32 months and 75% within 12 months, respectively (Eder *et al*., 2006; Celis *et al*., 2007). Moreover, the usual delayed effect of radiosurgery was not a limitation in the published reports for other radiosurgical functional indications including epilepsy (McGonigal *et al*., 2017).

The presence of other intact commissural fibres can explain the residual mild seizures after radiosurgery. It has been hypothesized that the neuropsychological side effects may also be less pronounced if some of the corpus callosum fibres are preserved (Lassonde and Sauerwein, 1997), which may be an advantage with incomplete destruction by gamma knife surgery.

Radiation exposure of extracranial organs is very low during LINAC radiosurgery (Maarouf *et al*., 2005) and particularly with gamma knife even in pregnant women (Paulsson et al., 2017). The level of external radiation is sufficiently low that some centres have considered installing a glass window in the treatment vault.

Based on our current experience and the literature (*table 1*) regarding GK-C, the following conclusions can be made:

– improvement was comparable to that with open surgery;
– there were no neurological consequences, such as disconnection syndrome;
– side effects were infrequent, transient and mild;
– a step-wise strategy was used for extension of callosotomy;
– adjunctive treatment was given to patients with hemispherotomy.

Conclusion

This case report highlights the importance of posterior extension and completion of callosotomy following unsatisfactory open anterior callosotomy. Moreover, gamma knife radiosurgery can offer an appropriate safe and effective alternative to open posterior callosotomy with relatively rapid response and without the cumulative risks associated with repeated open surgery. □

Disclosures.
None of the authors have any conflict of interest to declare.

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