Epileptic Disord 2011; 13 (2): 202-8

Corpus callosotomy with gamma knife radiosurgery for a case of intractable generalised epilepsy

Mohammad Bodaghabadi [1], Mohammad Ali Bitaraf [2], Shima Aran [3], Mazdak Alikhani [2], Hossein Ashrafian [4], Alireza Zahiri [5], Mahmud Alahverdi [6]

[1] Department of Radiology, Emam Khomeini hospital, Tehran University of Medical Sciences (TUMS) and Iran Gamma Knife Center
[2] Department of Neurosurgery, Tehran University of Medical Sciences (TUMS) and Iran Gamma Knife Center
[3] Department of Radio-Surgery, Emam Khomeini hospital, Tehran University of Medical Sciences (TUMS) and Iran Gamma Knife Center
[4] Department of Neurology, Tehran University of Medical Sciences (TUMS)
[5] Department of Radiology, Tehran University of Medical Sciences (TUMS)
[6] Department of Medical Physics and Biomedical Engineering, Tehran University of Medical Sciences, Tehran, Iran

Received January 20, 2011; Accepted May 1, 2011

ABSTRACT – Gamma knife radiosurgery is a minimally invasive procedure which can be used for patients with intractable epilepsies as an alternative for surgical corpus callosotomy. We report a 13-year-old boy with intractable epilepsy who underwent radiosurgical callosotomy. The patient demonstrated significant clinical improvement after gamma knife radiosurgery and was free of seizures 10 months after the procedure. However, He developed four short focal seizures with clonic movements during the 20 months post radiosurgery. Corpus callosotomy decreased epileptiform discharges in both hemispheres, indicating a role for the callosal neurons to facilitate an asymmetric epileptogenic susceptible state within the two hemispheres such that bisynchronous and bisymmetrical epileptiform discharges develop. Our result demonstrates that this novel therapeutic approach is a safe and effective option for the treatment of intractable generalised epilepsies.

Key words: gamma knife radiosurgery, callosotomy, generalised epilepsy

Correspondence:
M. A. Bitaraf
Department of Neurosurgery,
School of Medicine,
Tehran University of Medical Sciences,
No: 223 Vahid Dastgerdi (Zafar)Ave,
Tehran, Iran
<tums.research.center@gmail.com>

Open surgery is not an effective therapeutic approach for patients with medically intractable epilepsy with multifocal origins of epileptic activity who are not appropriate candidates for focal resections (Celis *et al*., 2007). The surgical approach to treat epilepsy is costly and associated with approximately 1% mortality and 10-20% morbidity rates especially when lesions are multifocal or located in deep or eloquent areas of the brain (Pilcher and Rusyniak, 1993). Corpus

doi:10.1684/epd.2011.0436

callosotomy is indicated in patients with severe medically intractable epilepsy in order to prevent bilateral synchronous epileptiform discharges and retard the rapid spread of epileptic activity between the two cerebral hemispheres (Eder *et al*., 2006). This method is noticeably effective for clonic, absence, myoclonic, simple and complex partial seizures (Cendes *et al*., 1993; Fuiks *et al*., 1991; Gates *et al*., 1992; Reutens *et al*., 1993; Spencer, 1988). Corpus callosotomy acts as a palliative therapeutic method, to decrease the frequency and severity of intractable epilepsies in order to diminish patients' disability (Pendl *et al*., 1999).

Although morbidity and mortality rates associated with open surgery are markedly reduced using the gamma knife (GN) radiosurgical approach, complications are still reported (Cendes *et al*., 1993; Oguni *et al*., 1991). There are important and life-threatening complications associated with open surgical callosotomy, including: infection (1-12%), intracranial haematomas (1-10%), brain oedema/swelling (0-3%), stroke (0-1.5%), and death (0-2.8%) (Lin *et al*., 2011). Hence, an alternative treatment with reduced side effects is essential. Although reports on GN radiosurgical corpus callosotomy in patients with intractable seizures are scarce in the literature (Celis *et al*., 2007; Eder *et al*., 2006; Feichtinger *et al*., 2006; Pendl *et al*., 1999), there is evidence in support of this therapeutic approach as a feasible and effective treatment option.

Case study

The patient was a 13-year-old boy, born after a full-term pregnancy from non-consanguineous parents. He was born with hypoxia and low birth weight (1,700 g). Initially, his neonatal period and growth rate were normal. Previous head trauma following a fall from a height of 1.5 meters was reported by his mother. The patient presented with mild to moderate psychophysical retardation and right-sided mild spastic hemiparesis. The epileptic condition started at three to four years of age as complex partial seizures. He later developed different types of seizures, including: tonic, clonic, tonic-clonic and absence seizures. The patient suffered from an average of 10 to 15 seizures per day for three years.

Carbamazepine, vigabatrin, phenytoin, lamotrigine, clonazepam, tiagabine, valproic acid, topiramate and primidone had been used in various combinations without success. The electroencephalogram (EEG) analysis showed 1.5 to 2.5 hertz (Hz) bilateral epileptiform synchronous spike-wave activity, dominant over the parieto-occipital region *(figure 1)*. Computed tomography (CT) scans and magnetic resonance imaging (MRI) studies showed bilaterally multifocal sclerotic lesions (suggesting post-traumatic old infarcts) and encephalomalacia in the parieto-occipital region. All medical and therapeutic approaches were

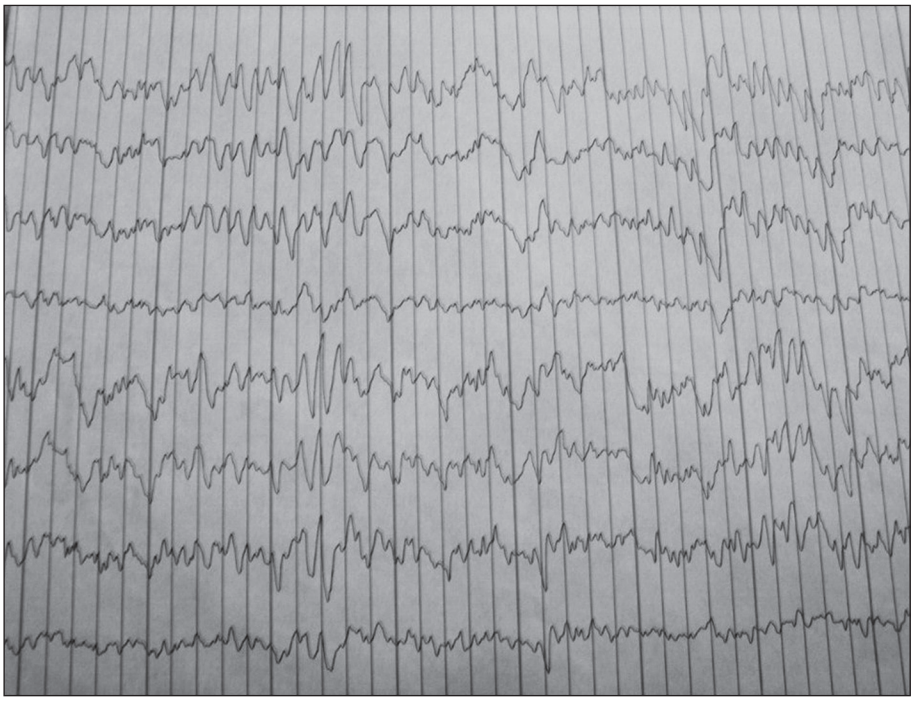

Figure 1. EEG with bilateral synchronous epileptiform spike-wave activity, dominant over the parieto-occipital region, compatible with generalised epilepsy.

unsuccessful during the past three years and he was not a suitable candidate for open surgical resection. Surgical callosotomy was offered as a therapeutic option and the patient's parents chose radiosurgery, scheduled in September 2009. A written informed consent was obtained from the parents for any scientific use of the registered medical data. The images used for corpus callosotomy were axial T1, T2, sagittal T2 and coronal T1-weighted, thin-sliced (1 mm) stereotactic MRI scans for 3-D volumetric reconstruction, using the planning software Leksell Gamma Plan (version 5.34; *figures 2, 3 and 4*). Six exposures with the 4-mm collimator helmet were glinted in the anterior or posterior part of the corpus callosum. The target to be irradiated was the rostrum, genu, and body of the corpus callosum, excluding the splenium (nearly total callosal disconnection). Stereotactic radiosurgery was performed at a maximum dose of 50.51 gray (Gy), with a marginal dose of 22.2 Gy on 99% perception isodose under local anaesthesia (Siegfried *et al*., 1998). The volume of the corpus callosum receiving the marginal dose at the 44% isodose line was 0.996 cm^3. The post-intervention hyper signal changes at the site of entrance of gamma knife beam to corpus callosum are depicted in *figure 5*. During the whole procedure, the patient was closely monitored by expert clinicians using video and audio devices. He was discharged the day after intervention without short-term complications. The patient demonstrated a significant clinical improvement after four and eight weeks in the follow-up visits and he was

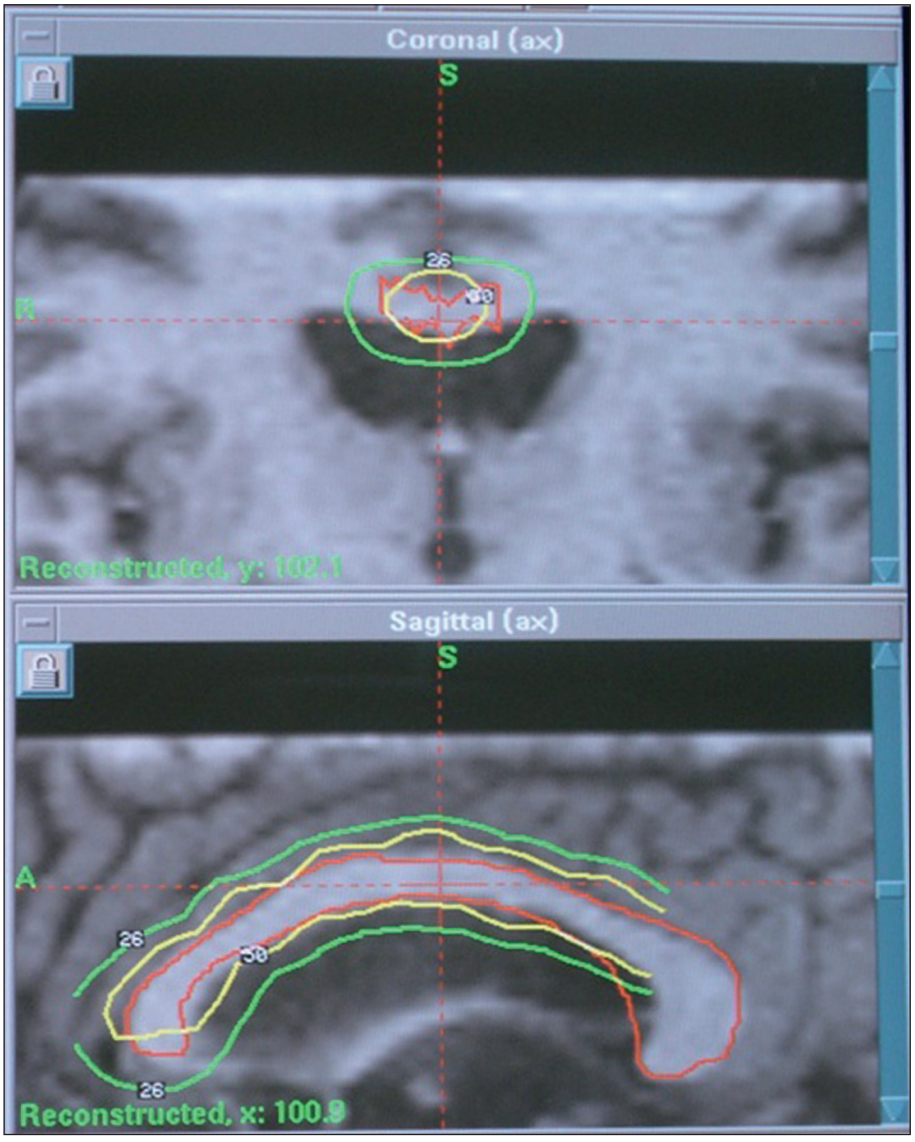

Figure 2. Corpus callosum borders were visualized by Leksell Gamma Plan at coronal and sagittal T1 views.

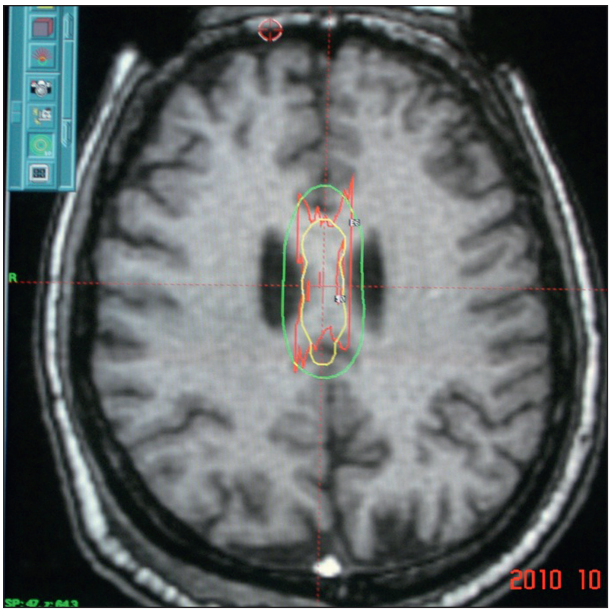

Figure 3. Corpus callosum borders were visualized by Leksell Gamma Plan at transversal T1 view.

visited on a regular basis. The corpus callosotomy by GN radiosurgery culminated in a reduction of seizure frequency and severity, generalised seizure pattern disappearance and transformation to focal or partial seizures. Ten months after radiosurgery, he was free of seizures, however, he developed four short focal seizures with clonic movements thereafter. The first seizure occurred ten months after the procedure. The second and third seizures occurred on the same day four months later and the last seizure took place five months after the second and third episodes. He did not have any further seizures until now (20 months after GN radiosurgery). The post-operative antiepileptic medications were 500 mg/day carbamazepine, 300 mg/day topiramate and 150 mg/day primidone which were tapered gradually over six months and were finally discontinued.

To assess the neuropsychological functions after GN radiosurgery, neuropsychological outcomes, including IQ, memory, language, executive functioning, attention, behaviour and subjective cognitive changes, were evaluated both before and ten months after surgery. For intelligence testing, the child was examined using a Wechsler Intelligence Scale for Children (Tewes, 1985). Short-term memory was assessed by digits forward and the Corsi block tapping task for numerical and spatial immediate memory span (Isaacs and Vargha-Khadem, 1989) and long-term memory was evaluated by a German version of the Auditory Verbal Learning Test for Verbal memory (Helmstaedter *et al.*, 2001). The token test was used as a screening test for aphasia. This test assesses sentence comprehension and is a commonly used language test in children and adults (Orgass, 1982). Response inhibition and verbal fluency were included as tests for executive functions. Attention in terms of processing speed was assessed with a letter cancellation test which requires crossing target letters among distracters within a limited time frame (Brickenkamp, 1968). All the test results indicated a satisfactory neuropsychological outcome compared to data before the procedure. Mental and physical status, as well as function in school, improved significantly. Moreover, the parents experienced a meaningful amelioration in his quality of life.

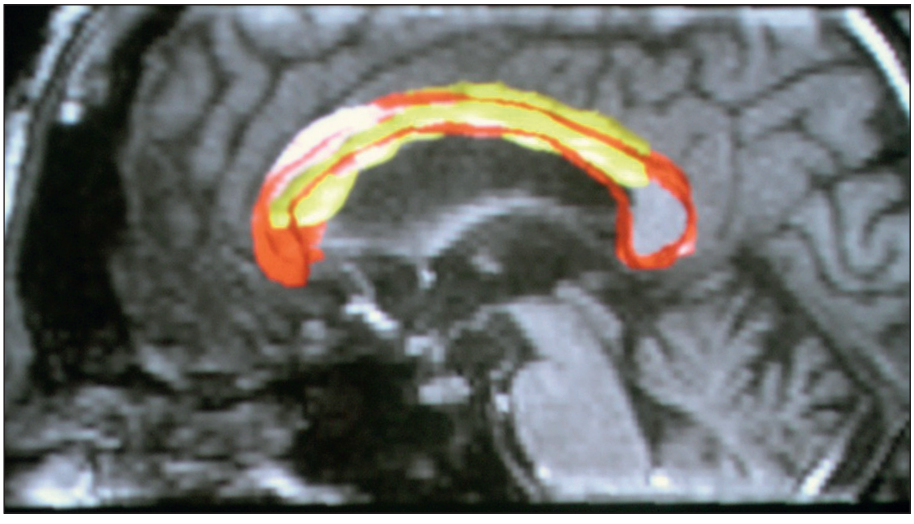

Figure 4. Corpus callosum borders were visualized by Leksell Gamma Plan at sagittal T1 view.

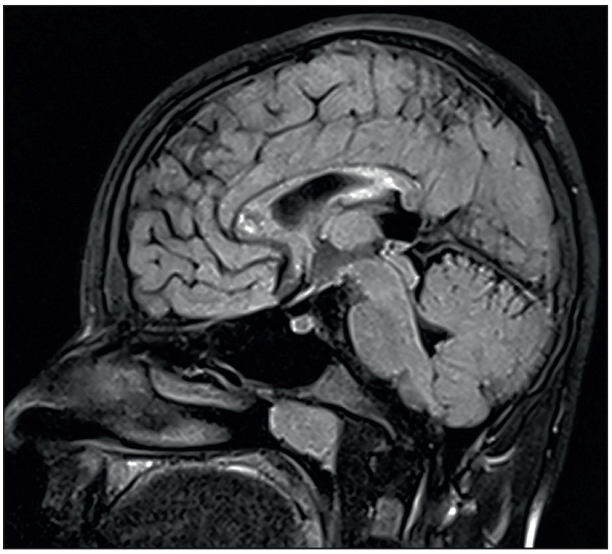

Figure 5. Hyper signal changes at the site of entrance of the gamma knife beam to the corpus callosum, visualized at sagittal flare view.

Discussion

The corpus callosum is a major pathway of epileptiform discharge transmission from one hemisphere to another and callosotomy may interrupt propagation of epileptiform discharges between the two hemispheres. The first results of corpus callosotomy were reported by Van Wagenen and Herren in 1940 on 10 patients (Van Wagenen and Herren, 1940). Several studies support the theory of a reduction in bilateral and bisynchronous epileptiform discharge after disruption of pathways between the two hemispheres. The frequency of seizures has been reported to decrease from 80% to 70% following open surgical callosotomy in patients with intractable epilepsies (Cendes *et al*., 1993; Fuiks *et al*., 1991; Gates *et al*., 1984; Gates *et al.,* 1987; Oguni *et al*., 1994; Oguni *et al*., 1991; Reutens *et al*., 1993). Although not all epileptiform discharges may be affected by this procedure, the incomplete distribution of bilateral synchronous interictal epileptiform discharges and disruption of their flow pathways may give rise to complete suppression of generalised epilepsy and normalisation of brain EEGs (Baba *et al*., 1996; Gates *et al*., 1987; Spencer *et al*., 1993).

The patient in our study suffered with intractable epilepsy and frequent drop attacks and the generalised epilepsy resulted in severe disability and significant decline in his quality of life. Therefore, finding an effective therapeutic approach to reduce his epileptic attacks was of great significance in order to improve his performance and quality of life.

The idea of using radiotherapy for the treatment of epilepsy is not novel. In 1939, Tracy designed the method of X-ray radiation in conjunction with bromide for the first time (Tracy, 1905) and seventy patients with intractable epilepsies were treated with external beam irradiation by Von Wieser (Wieser, 1939). GN was introduced by Leksell in 1950 for functional neuroradiosurgery. This procedure was primarily used to treat tumours and vascular malformations (Leksell, 1983). Some studies have proposed radiosurgery as a valuable option for irradiation of focal epileptic targets (Dunoyer *et al*., 2002). In patients with deep-seated epileptic foci that are difficult to access, GN was used to irradiate the targets (Hellstrand *et al*., 1993). Approximately 50% to 83% of patients with epilepsies who underwent radiosurgery had a significant reduction in epilepsy after resective surgery (Falkson *et al*., 1997; Schröttner *et al*., 1998). Following stereotactic radiosurgery for seizures arising from the temporal lobe, the patient may become seizure-free. Seizure control after radiosurgery in children is similar to that in adults (Régis *et al*., 2000; Régis *et al*., 1995; Régis and Roberts, 1999). The major concern for children is the risk of long-term irradiation side effects, however these are dose dependent. Since the irradiation of targets is achieved using low doses, the risk of tissue injury is very low. Doses that suppress epileptic foci are reported to range from 10 to 20 Gy and are lower than those that cause necrosis (Barcia-Salorio *et al*., 1987; Heikkinen *et al*., 1992; Mori *et al*., 2000; Whang and Kwon, 1996). Today, GN radiosurgery is an alternative adjunct to open surgery based on its effect on reducing epilepsy and significantly improving patients' quality of life. However, according to previous studies on callosotomy, there tends to be some deterioration in seizure control after two years (Pressler *et al*., 1999). Vagal nerve stimulation (VNS) is also another alternative treatment option which has proven to be effective against medically intractable epilepsy in both adults and children for whom brain surgery is not indicated or has failed. VNS reduces seizure susceptibility of the cerebral cortices. However, there are also some complications associated with this procedure, including: infection, lead fracture, fluid collection around the stimulator, neck pain and difficulty swallowing (Kabir *et al*., 2009). Although the effect of VNS on seizures is less dramatic, the less invasive nature and wide range of indication have made VNS indispensable as an alternative treatment for the comprehensive care of epilepsy (Kawai, 2007).

The concept of treatment of multifocal-induced epilepsies by radiosurgery is novel and, to our knowledge, there are few reports in the literature that describe corpus callosotomy using stereotactic radiosurgery (Celis *et al*., 2007; Eder *et al*., 2006; Feichtinger *et al*., 2006; Pendl *et al*., 1999). In 1999, the first report

of corpus callosotomy for the treatment of patients with multifocal refractory epilepsies was published by Pendl (Pendl *et al*., 1999). They used radiosurgery to ablate the anterior part of the corpus callosum in three patients (with mean age of 27.6 years) with intractable epilepsy and performed radiosurgery with a cobalt-60, in two stages with 50 Gy and then 170 Gy at maximum. In 2006, two series of three and eight cases were reported at the Graz University by Eder *et al*. (2006) and Feichtinger *et al*. (2006), respectively. They used GN to disrupt the anterior third of the corpus callosum and performed GN with marginal dose of 55-60 Gy on the 50% isodose. A reduction of 60% and 100% in epilepsy drop attacks and generalised epilepsies were reported, respectively.

In 2007, Celis *et al*. reported a 17-year-old male patient who underwent corpus callosotomy with a prescribed dose of 36.0 Gy at the periphery of the rostrum, genu, and one half of the body of the corpus callosum (CCA). Their results showed an improvement rate of 84% for drop attacks and generalised tonic-clonic seizures after 32 months of follow-up (Celis *et al*., 2007). They concluded that radiosurgical callosotomy was an effective and noninvasive approach, in contrast to the alternative invasive treatment options. In this method, a section along the corpus callosum is reproduced by GN (*figure 3*) to prevent bilaterally synchronous epileptiform discharges, propagating to the contralateral hemispheres and with lower transient and permanent complications reported from open surgery (Lassonde and Sauerwein, 1997; Quattrini *et al*., 1997; Rossi *et al*., 1996).

According to our findings, corpus callosotomy using GN radiosurgery significantly improved symptoms in our patient. This novel therapeutic approach is therefore a safe and effective option for the treatment of carefully selected cases of medically intractable epilepsy. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

References

Baba H, Ono K, Matsuzaka T, Yonekura M, Teramoto S. Surgical results of anterior callosotomy on medically intractable epilepsy. Paper presented at the World Congress of the International College of Surgeons, 1996.

Barcia-Salorio JL, Vanaclocha V, Cerdá M, Ciudad J, López-Gómez L. Response of experimental epileptic focus to focal ionizing radiation. Appl Neurophysiol 1987; 50: 359-64.

Brickenkamp R. Test d2 Aufmerksamkeits-Belastungs-Test. Göttingen: Hogrefe Verlag, 1968.

Celis MA, Moreno-Jiménez S, Lárraga-Gutiérrez JM, *et al*. Corpus callosotomy using conformal stereotactic radiosurgery. Childs Nerv Syst 2007; 23: 917-20.

Cendes F, Ragazzo PC, da Costa V, Martins LF. Corpus callosotomy in treatment of medically resistant epilepsy: Preliminary results in a pediatric population. Epilepsia 1993; 34: 910-7.

Dunoyer C, Ragheb J, Resnick T, *et al*. The use of stereotactic radiosurgery to treat intractable childhood partial epilepsy. Epilepsia 2002; 43: 292-300.

Eder HG, Feichtinger M, Pieper T, Kurschel S, Schroettner O. Gamma knife radiosurgery for callosotomy in children with drug-resistant epilepsy. Childs Nerv Syst 2006; 22: 1012-7.

Falkson CB, Chakrabarti KB, Doughty D, Plowman PN. Stereotactic multiple arc radiotherapy: influence of treatment of arteriovenous malformations on associated epilepsy. Br J Neurosurg 1997; 11: 12-5.

Feichtinger M, Schröttner O, Eder H, *et al*. Efficacy and safety of radiosurgical callosotomy: a retrospective analysis. Epilepsia 2006; 47: 1184-91.

Fuiks KS, Wyler AR, Hermann BP, Somes G. Seizure outcome from anterior and complete corpus callosotomy. J Neurosurg 1991; 74: 573-8.

Gates JR, Leppik IE, Yap J, Gumnit RJ. Corpus callosotomy: Clinical and electroencephalographic effects. Epilepsia 1984; 25: 308-16.

Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE. Response of multiple seizure types to corpus callosum section. Epilepsia 1987; 28: 28-34.

Gates JR, Wada JA, Reeves AG, *et al*. Reevaluation of corpus callosotomy. In: Engel J Jr. *Surgical Treatment of the Epilepsies, Second Edition*. New York: Raven Press, 1992: 637-48.

Heikkinen ER, Heikkinen M, Sotaniemi K. Stereotactic radiotherapy instead of conventional epilepsy surgery: a case report. Acta Neurochir (Wien) 1992; 119: 159-60.

Hellstrand E, Abraham-Fuchs K, Jernberg B, *et al*. MEG localization of interictal epileptic focal activity and concomitant stereotactic radiosurgery: a non-invasive approach for patients with focal epilepsy. Physiol Meas 1993; 14: 131-6.

Helmstaedter C, Lendt M, Lux S. VLMT: Verbaler Lern- und Merkfähigkeitstest. Göttingen: Beltz Test, 2001.

Isaacs EB, Vargha-Khadem F. Differential course of development of spatial and verbal memory span: a normative study. *Br J Dev Psychol* 1989; 7: 377-80.

Kabir SM, Rajaraman C, Rittey C, Zaki HS, Kemeny AA, McMullan J. Vagus nerve stimulation in children with intractable epilepsy: indications, complications and outcome. Childs Nerv Syst 2009; 25: 1097-100.

Kawai K. Less invasive treatment of intractable epilepsy- vagus nerve stimulation and stereotactic radiosurgery. Brain Nerve 2007; 59: 299-311.

Lassonde M, Sauerwein C. Neuropsychological outcome of corpus callosotomy in children and adolescents. J Neurosurg Sci 1997; 41: 67-73.

Leksell L. Stereotactic radiosurgery. J Neurol Neurosurg Psychiatry 1983; 46: 797-803.

Lin JS, Lew SM, Marcuccilli CJ, *et al*. Corpus callosotomy in multistage epilepsy surgery in the pediatric population. J Neurosurg Pediatr 2011; 7: 189-200.

Mori Y, Kondziolka D, Balzer J, *et al*. Effects of stereotactic radiosurgery on an animal model of hippocampal epilepsy. Neurosurgery 2000; 46: 157-65; discussion: 165-8.

Orgass B. Token test, manual. Weinheim: Beltz Test, 1982.

Oguni H, Olivier A, Andermann F, Comair J. Anterior callosotomy in the treatment of medically intractable epilepsies: A study of 43 patients with a mean follow-up of 39 months . Ann Neurol 1991; 30: 357-64.

Oguni H, Andermann F, Gotman J, Olivier A. Effect of anterior callosotomy on bilaterally synchronous spike and wave and other EEG discharges. Epilepsia 1994; 35: 505-13.

Pendl G, Eder HG, Schroettner O, Leber KA. Corpus callosotomy with radiosurgery. Neurosurgery 1999; 45: 303-7; discussion: 307-8.

Pilcher WH, Rusyniak WG. Complications of epilepsy surgery. Neurosurg Clin N Am 1993; 4: 311-25.

Pressler RM, Binnie CD, Elwes RD, Polkey CE. Return of generalized seizures and discharges after callosotomy. Adv Neurol 1999; 81: 171-82.

Quattrini A, Del Pesce M, Provinciali L, *et al*. Mutism in 36 patients who underwent callosotomy for drug-resistant epilepsy. J Neurosurg Sci 1997; 41: 93-6.

Régis J, Roberts DW. Gamma knife radiosurgery relative to microsurgery: epilepsy. Stereotact Funct Neurosurg 1999; 72: 11-21.

Régis J, Peragui J, Rey M, *et al*. First selective amygdalohippocampal radiosurgery for mesial temporal lobe epilepsy. Stereotact Funct Neurosurg 1995; 64: 193-201.

Régis J, Bartolomei F, Hayashi M, Roberts D, Chauvel P, Peragut JC. The role of gamma knife surgery in the treatment of severe epilepsies. Epileptic Disord 2000; 2: 113-22.

Reutens DC, Bye AM, Hopkins IJ, *et al*. Corpus callosotomy for intractable epilepsy: Seizure outcome and prognostic factors. Epilepsia 1993; 34: 904-9.

Rossi GF, Colicchio G, Marchese E, Pompucci A. Callosotomy for severe epilepsies with generalized seizures: outcome and prognostic factors. Acta Neurochir (Wien) 1996; 138: 221-7.

Schröttner O, Eder HG, Unger F, Feichtinger K, Pendl G. Radiosurgery in lesional epilepsy: brain tumors. Stereotact Funct Neurosurg 1998; 70: 50-6.

Siegfried J, Haller D, Heinzel F, *et al*. Gamma knife radiosurgery in neurosurgery. Schweiz Med Wochenschr 1998; 128: 115-22.

Spencer SS. Corpus callosum section and other disconnection procedures for medically intractable epilepsy. Epilepsia 1988; 29: S85-99.

Spencer SS, Katz A, Ebersole J, Novotny E, Mattson R. Ictal EEG changes with corpus callosum section. Epilepsia 1993; 34: 568-73.

Tewes U. Hamburg–Wechsler Intelligenztest für Kinder, Revision 1983. Bern: Huber, 1985.

Tracy SG. High-frequency high potential currents, and X-radiations in the treatment of epilepsy. *N York Med J* 1905: 81: 422-4.

Van Wagenen WP, Herren RY. Surgical division of commissural pathways in the corpus callosum: Relation to spread of an epileptic attack. *Arch Neurol* 1940; 44: 740-59.

Whang CJ, Kwon Y. Long-term follow-up of stereotactic gamma knife radiosurgery in epilepsy. Stereotact Fun ct Neurosurg 1996; 66: 349-56.

Wieser W. Die Röntgentherapie der traumatischen Epilepsie. *Mschr Psychiat Neurol* 1939; 101: 171-9.