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

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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 bismmetrical 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

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
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 cm³. 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.
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.
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 neuro-radiosurgery. 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; Heikinen 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

Discussion

The corpus callosum is a major pathway of epilepticiform 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; Fuks 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.

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


