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REVIEW

Non-resective surgery and radiosurgery for treatment of drug-resistant epilepsy

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Summary   Epilepsy surgery is an effective treatment for properly selected patients with intractable seizures. However, many patients with medically intractable epilepsy are not excellent candidates for surgical resection of the epileptogenic zone. Due to recent advances in computer technology and bioengineering, several novel techniques are receiving increasing interest for their role in the care of people with epilepsy. Neuromodulation is an emerging surgical option to be used when conventional resective surgery is not indicated. We review the indications and expected outcomes of neuromodulatory treatments currently available for the treatment of refractory epilepsy, i.e., vagus nerve stimulation, deep brain stimulation, stereotactic radiosurgery, and multiple subpial transections.
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Contents

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Introduction

Epilepsy is a relatively common chronic neurological disorder affecting approximately 1% of the population worldwide (about 50,000,000 people). The initial response to therapy is usually highly predictive of long-term outcome (Kuzniecky and Devinsky, 2007; Go and Snead, 2008). Unfortunately, despite medical treatment with antiepileptic drugs (AEDs), up to 30% of patients continue to have seizures (Kuzniecky and Devinsky, 2007; Go and Snead, 2008). Intractable seizures may lead to a progressive disorder that is medically, physically, and socially disabling (Kuzniecky and Devinsky, 2007; Go and Snead, 2008; Cascino, 2004).

Epilepsy surgery is a highly effective option for selected patients with intractable epilepsy and has witnessed a dramatic growth over the last two decades, due to advances in electrophysiology, neuroimaging, neurointensive care, and neuroanesthesia, as well as to a better understanding of basic mechanisms of epilepsy (Go and Snead, 2008; Cascino, 2004; Noachtar and Borggraefe, 2009). It is estimated that more than 5,000,000 individuals worldwide are potential candidates for epilepsy surgery. The correct identification of these patients, methods for localization of seizure focus, and outcome measures are discussed in detail elsewhere (Kuzniecky and Devinsky, 2007; Go and Snead, 2008; Cascino, 2004; Noachtar and Borggraefe, 2009). Surgical treatment of epilepsy surgery includes a wide and heterogeneous array of procedures ranging from excisional microsurgery (such as mesial temporal lobe resection and selective amygdalohippocampectomy) to more recent and less invasive procedures of neuromodulation. Resective surgery is performed when a satisfactory localization of the seizure focus is achieved using a convergence of evidence from multiple sources (i.e., neurological examination, seizure semiology, EEG, MRI, etc.). The goal is to remove the cortical region from which seizure originate without causing neurological complications. Detection of multiple independent seizure foci is a contraindication to resective surgery, with few exceptions. Moreover, seizure foci located in close vicinity to eloquent cortex is much more difficultly approached by resective surgery even when cortical mapping is used (Bauman et al., 2005; Devinsky et al., 2003).

Due to recent advances in computer technology and bioengineering, several newer techniques have received increased interest in epilepsy care. Neuromodulation is an emerging surgical option to be used when resective surgery is not indicated (Anderson et al., 2009; Saillet et al., 2009). It includes the delivery of electrical stimulation to selected brain regions or to the vagus nerve as well as stereotactic radiosurgery, multiple subpial transections, and the more recent generation of neurostimulators. Neuromodulation is commonly reserved for patients excluded from resective surgery due to poor localization of the epileptic zone, multiple foci, foci in close proximity to eloquent cortex, or deep brain regions requiring aggressive and risky surgical approaches.

In this paper we review the indications and expected outcome of the following neuromodulatory treatments: vagus nerve stimulation, deep brain stimulation, stereotactic radiosurgery, and multiple subpial transections.

Vagus nerve stimulation

Beginning in the 1930–1940s experiments suggested vagus nerve stimulation (VNS) could affect EEG expression and seizure frequency in animal models of epilepsy (Bailey and Bremer, 1938). Further studies demonstrated the potential usefulness of this approach in the treatment and prevention of seizures in dogs (Zabara, 1985, 1987). The left vagus nerve is principally composed of afferent fibers connecting visceral receptors to several CNS structures through an intermediate relay station in the brainstem (nucleus tractus solitarius). It has been hypothesized that the train of stimulation carried trough the nerve desynchronizes electrical neuron activity in multiple brain site (Theodore and Fisher, 2004; Mapstone, 2008). 18FDG PET and MRI functional studies in patients treated with VNS have shown a pattern of metabolic activation in the dorsal medullary vagus system (nucleus tractus solitarius, locus coeruleus and raphe nuclei) as well as in the inferior cerebellum, hypothalamus, bilateral thalami, and insular cortices with decreased activity in the areas of the hippocampus, amygdala and cingulate gyrus (Bohning et al., 2001; Sucholeiki et al., 2002). There is also some evidence of norepinephrine and to a lesser degree serotonin as being fundamental to the mechanism of action of VNS (Ben-Menachem et al., 1995). Overall, the mechanism of action of VNS is still not fully understood and its use is based on the empirical observation of its clinical efficacy.

VNS was approved for the treatment and prevention of refractory seizures in adults and adolescents by the European and US regulatory boards in 1994 and 1997, respectively. Vagus nerve stimulation is achieved by a device manufactured and supplied by Cyberonics, Inc., in which a pulse generator source, surgically implanted in a subclavicular pouch, is connected to two helical bipolar stimulating electrodes placed around the left vagus nerve distal to its principal efferent branches to minimize vegetative (mainly cardiovascular) side effects (McGregor et al., 2005). Since the first implant (Penry and Dean, 1990) in 1988 many epilepsy centres have adopted this neuromodulatory technique as part of their armamentarium for the treatment of refractory epilepsy. In the U.S. alone, over 13,000 VNS procedures were performed between the 1998 and the 2005 (Baaj et al., 2008). The long term safety of VNS and its limited and well tolerated side effects have been widely demonstrated (Baaj et al., 2008; Ben-Menachem et al., 1999; Uthman et al., 2004; Benifla et al., 2006).

Initial reports on VNS treatment suggested an efficacy to an extent similar to that obtained with newly marketed

AEDs. Moreover, further reduction of seizure frequency was reported with long-term treatment, even after 1 year. However, longer follow-up did not confirm the initial impressive effect with less than 2% of patients becoming seizure-free after VNS (Mapstone, 2008). Nevertheless, between 35 and 45% of patients experience a reduction exceeding the 50% in the baseline seizure frequency. In these subjects, VNS has a significant impact on neurological function, social, mood, behaviour scores, and reduction in the pharmacological therapy (Baaj et al., 2008; Ben-Menachem et al., 1999; Uthman et al., 2004). In addition, the profile of adverse effects can be considered minimal with postoperative infection occurring in 3—6% of patients, most of them treated with oral antibiotics and rarely requiring pulse generator or electrode removal. Relatively common side effects include dysphonia (20—30%) and cough (6%), but are usually transient and related to the intensity of stimulation (Ben-Menachem et al., 1999; Uthman et al., 2004). Sleep apnea or other clinically significant cardiopulmonary dysfunction is much rarer.

These characteristics have lead to the relatively widespread use of VNS including for children below 12 years age after the demonstration of the safety profile also in this age population (Benifla et al., 2006). This shift to an earlier age of implantation has been triggered by the earlier identification of pharmacological refractory cases and by the prospective that a significant improvement in quality of life and theoretically brain development could be obtained by a reduction in seizure frequency (Murphy et al., 2003). Preliminary published results as well as our own experience suggests a role for VNS in the treatment of some of the most difficult to treat pediatric epilepsy syndromes, such as Lennox—Gastaut syndrome (Frost et al., 2001), epilepsy associated with tuberous sclerosis (Parain et al., 2001), and hypothalamic hamartoma-gelastic epilepsy (Murphy et al., 2003).

It is still unclear which patient groups are most likely to benefit from VNS with a minority of patients achieving a seizure control that significantly affects their quality of life and full seizure freedom being rare. Therefore, VNS should generally be reserved for patients who are not candidates for resective surgery, or those in whom surgical intervention has failed. The main advantages of VNS are the low surgical risk and the lack of significant toxicity or adverse drug interaction.

Deep brain stimulation

Deep brain stimulation (DBS) has been shown to be highly effective in the treatment of movement disorders with more than a decade of widespread use. DBS for epilepsy is a more recent and evolving treatment approach. There is currently not a consensus regarding the best brain targets and stimulation parameters for an individual patient. To date, stimulated structures have included the anterior or centromedian nucleus of the thalamus, subthalamic nucleus, caudate nucleus, hippocampus, hypothalamus, cortex, and cerebellum, resulting in variable effects on seizures (Ellis and Stevens, 2008).

The precise mechanism through which DBS exert its effect is still debated, especially the question of whether stimulation modulates the pathological epileptic network or, as postulated for movement disorders, the final effect is related to a reversible microlesional mechanism (Van Roost et al., 2007).

Animal and human data support the view that brain stimulation can abort epileptiform activity (Stacey and Litt, 2008). Since the 1940s the thalamus has been considered to have a central role in epilepsy, even being referred to as the ''pacemaker for the cortex'' (Penfield and Jasper, 1954). The anterior (ANT) and centromedian (CMT) nuclei have been targets for stimulation. The ANT is part of the Papez's circuit which has been demonstrated in animal models to have a role in the propagation of seizures. Moreover, the stimulation of ANT can block generalized seizures induced by pentylenetrazol, putatively through interference with mammillothalamic projections (Mirski and Ferrendelli, 1986).

Bilateral ANT stimulation was originally pioneered in small pilot trials on patients with either generalized or focal epilepsy (Andrade et al., 2006; Hodaie et al., 2002; Kerrigan et al., 2004; Lee et al., 2006; Osorio et al., 2007; Upton et al., 1985). In all studies, the safety and tolerability of the implant were demonstrated, with some authors using microelectrode recording to optimize targeting and providing a correlation with intraoperative EEG recordings (Velasco et al., 2001). However, the outcome was variable with seizure reduction ranging between 24% and 89%. No difference emerged between cycling or continuous high frequency stimulation, although stimulation parameters varied between the different studies. In 2010 a multicenter double-blinded randomized study involving over 100 subjects was reported (Blount et al., 2004). Median declines in seizures were 40.5% in the stimulated group compared with 14.5% in the control group. Furthermore ''most severe'' seizures were significantly reduced by stimulation. At 2 years, there was still a 56% median percent reduction in seizure frequency and 54% of patients had a seizure reduction of at least 50% while 14 patients had become seizure-free for at least 6 months. Mortality was significant with five deaths, although none were apparently related to implantation or stimulation.

CMT has direct projections to the cortex and it is hypothesized that CMT DBS can induce hyperpolarization and lead to a desynchronization of the ascending reticular and cortical neurons (Velasco et al., 2001). CMT-DBS has been used with good results also in focal epilepsy with secondary generalization (Velasco et al., 1987) and in Lennox—Gastaut syndrome (Velasco et al., 2006). An early placebo-controlled study of CMT for the treatment of medication refractory seizures showed good safety and modest efficacy (Shimizu and Maehara, 2000).

The subthalamic nucleus (STN) is considered the principal target for DBS in movement disorders and has become widely adopted for this indication (Tabbal et al., 2007). STN has been proposed as a possible therapeutic target in refractory epilepsy, based on the knowledge that the inhibition of the excitatory effect of the substantia nigra pars reticulata (SNr) can reduce the firing of the γ-aminobutyric acid neurons in the deep layer of superior colliculus, i.e., the dorsal midbrain anticonvulsant zone (DMAZ) (Iadarola and Gale, 1982; Gale, 1986). The first successful and effective STN-DBS for epilepsy was reported by Benabid et al. (2001) in a child with cortical dysplasia. Subsequently, other neurosurgeons

have performed STN electrode implantation with overall seizure reduction ranging between 60% and 80% in refractory focal epilepsies (Chabardes et al., 2002; Dinner et al., 2002; Vonck et al., 2003; Shon et al., 2005), and a lower efficacy (50% seizure reduction) in progressive myoclonic epilepsy (Vesper et al., 2007). However, so far only a limited number of patients have received STN-DBS and additional trials are required to asses its therapeutic potential and indications.

Integral components of Papez's circuit, and also the most epileptogenic areas of the brain, the hippocampus and amygdala are natural choices for any intervention aimed at the source or propagation path of seizures (Oikawa et al., 2001). Standard microsurgical resection of these areas results in post-operative long lasting resolution of seizures in up 75% of patients of properly selected patients (Schramm, 2008). Hippocampal DBS has been used experimentally for poor candidates for resective surgery, such as those with bilateral ictal localization or in whom preoperative neurophysiological findings (e.g., Wada test) predict a post-operative decline in critical brain functions. In these cases, the hippocampus is stimulated continuously using high-frequency square-wave pulses. The reduction of inter-ictal spike activity during a period of acute stimulation is the criterion for deciding whether the leads will be connected to an internal pulse generator (Van Roost et al., 2007; Boon et al., 2007). No major side effects or neurophysiological changes have been reported with this approach but the outcome on seizure frequency is quite variable (Stevens et al., 1969). Cerebellum was one of the earliest studied structures for stimulation in epilepsy patients but controlled studies showed a modest efficacy and it has not been widely adopted (Davis and Emmonds, 1992; Cooper et al., 1976). The caudate and other brain regions have been postulated as areas for brain stimulation to improve epilepsy (Chkhenkeli and Chkhenkeli, 1997; Fountas et al., 2010), but much clinical research is required before any conclusions can be drawn.

New-generation neurostimulators

While the brain stimulation techniques described above (in particular, DBS) are encouraging, their use is unlikely to lead to a high rate of seizure freedom among patients who have failed other treatments. Advances in seizure prediction now promise to give rise to implantable devices able to warn of impending seizures and to trigger therapy to prevent clinical epileptic attacks (Litt, 2003; Sun et al., 2008). Responsive stimulation aims to suppress epileptiform activity by delivering stimulation directly in response to electrographic activity. Animal and human data support the concept that responsive stimulation can abort epileptiform activity, and this modality may be a safe and effective treatment option for epilepsy. Responsive stimulation has the great advantage of specificity, as it can be targeted to the specific brain regions involved in the seizure. In addition, responsive stimulation provides temporal specificity. Treatment is provided as needed, potentially reducing the likelihood of functional disruption or habituation due to continuous treatment (Litt and Echauz, 2002).

Current epileptic seizure ''prediction'' algorithms are generally based on the knowledge of seizure occurring time and analyze the EEG recordings retrospectively. It is then

obvious that, although these analyses provide evidence of brain activity changes prior to epileptic seizures, they cannot be applied to develop implantable devices for diagnostic and therapeutic purposes. An optimal alternative approach to the open-loop device — in which continuous electrical stimulation is used — is a closed-loop or ''intelligent brain device''. This closed-loop device would produce a burst of stimulation only in response to specific recorded brain electrical activity. Thus, the goal with this method is to have a device which can recognize specific brain discharges which indicate a high risk for evolution to the point of clinical seizure, so that the device would stop their propagation. Such an approach would have reduced daily doses of stimulation leading to longer battery life and, possibly, a better tolerability profile (Litt, 2003; Sun et al., 2008). At this point in time theoretical long-term safety concerns of kindling or apoptosis induced by exposure to continuous electrical current (Fountas et al., 2010) appear unwarranted, but certainly not out of the realm of possibility. A pilot trial of 4 patients with refractory seizures treated with responsive cortical stimulation showed suppression of clinical seizures and resolution of electrographic seizure activity (Kossoff et al., 2004). Recently, high-frequency stimulation was performed in eight patients with a closed-loop system, in which stimulation was delivered either to the epileptogenic cortex ($n = 4$) or ATN ($n = 4$) after automated seizure detection. Three out of the 4 cortical stimulation patients and two out of the 4 ATN DBS patients responded with decreased seizure frequency (Osorio et al., 2005). The RNS NeuroPace (Mountain View, CA) is an investigational implantable responsive neurostimulator system that is being evaluated in a multi-center, randomized, double-blinded trial to assess the safety and efficacy of responsive stimulation for the treatment of medically refractory epilepsy. The RNS IPG continuously analyzes the patient's electrocortigram and triggers stimulation whenever the characteristics programmed by the clinician are indicative of seizures or epileptiform precursors. A feasibility study of this closed loop device has already described approximately a 45% decrease in seizure frequency in the majority of patients at 9 months follow-up (Fountas et al., 2005). Although preliminary data are encouraging, whether closed-loop seizure-prediction and treatment devices will have the profound clinical effect of their cardiological predecessors will depend on our ability to perfect these techniques. Certainly, their clinical efficacy must be validated in large-scale, prospective, controlled trials.

Radiosurgery

Stereotactic radiosurgery (SRS) is an emerging neurosurgical technique which allows the delivery of multiple cross-fired beams generated from a highly collimated radiation source to a selected target localized trough an accurate stereotactic system. This non-invasive method has been widely used for treatment of several neurosurgical diseases and is a developing therapeutic approach for medically intractable epileptogenic foci (Romanelli and Anschel, 2006).

Devices for radiosurgery are based on gamma (gamma-knife) or X-ray sources (linear accelerator, LINAC) with or without the use of stereotactic frame to immobilize the patient head. Their most recent and advanced version can

shape the beam through a computer controlled multileaf collimation which allows better conformity to non-spherical targets. Most experience in the use of SRS for epilepsy is on epilepsy secondary to tumors, and arteriovenous malformation (AVM) or cavernomas, in which often the primary endpoint was not the improvement in seizure frequency. However, more recently, results have been published on SRS as the primary treatment of epilepsy secondary to mesial temporal sclerosis or hypothalamic hamartoma (Regis et al., 2000, 2004a; Romanelli et al., 2008).

The mechanism through which SRS exerts its therapeutic effect on seizures has not been entirely elucidated, but it is clear that seizure control does not entirely correlate with radiation-induced necrosis. A neuromodulatory rather than ablative effect is suggested by the fact that the dose clinically used is below that considered inducing necrosis as well as by post-treatment neuroimaging and pathology studies (Romanelli and Anschel, 2006; Regis et al., 1996; Srikijvilaikul et al., 2004).

Initial research on animal models has suggested that, after irradiation, epileptogenic cortex can undergo an alteration of neurotransmitters sufficient to stop pathological discharges but not normal neuronal activity (Regis et al., 2002). Although data from animal models should be applied with caution to humans, these findings support the usefulness of radiosurgery to preferentially affect epileptogenic versus normal cortex. While there is a waiting period of greater than one year to obtain the full effect of SRS for epilepsy, it has the advantages of being an outpatient procedure not requiring general surgical or anaesthesia risks. In addition to its use for epilepsy secondary to mesial temporal sclerosis, there appears to be a possibly stronger indication for SRS combination with surgery for epileptogenic tumors of the mesial temporal pole (Schrottner et al., 2002). The choice between open and noninvasive surgery should still be guided by the difficulties presented by the lesion rather than any epilepsy-specific characteristics of either surgical technique (Quigg and Barbaro, 2008).

Radiosurgery is under evaluation also as an alternative to open surgery for mesial temporal lobe epilepsy. However, outcome in terms of seizure remission is variable. The first trial exploring the efficacy of SRS in mesial temporal lobe epilepsy was published by Regis et al. (2004a). The initial changes on MRI were visualized about one year after treatment and clinical follow-up at two years demonstrated an overall significant clinical improvement and side effect profile comparable to that of standard temporal lobectomy. Other published series from different groups have shown somewhat variable results on seizure control (Romanelli et al., 2008), also due to different delivered radiation dose or follow-up time. In a recent prospective multicenter pilot trial, two different radiosurgery doses were compared and the overall seizure remission rate was 69% during the third follow-up year after treatment which is comparable to that reported for resective temporal lobectomy (Chang et al., 2010). However, further work is needed to clarify whether remission rates or neurocognitive outcomes after radiosurgery are comparable to those after anterior temporal lobectomy.

SRS is also increasingly being considered with good safety profile for the treatment of hypothalamic hamartomas (HHs), typically associated with pharmacologically intractable gelastic seizures and which often develop into complex partial and/or generalized tonic—clonic seizures. This surgery should be ideally performed in the early years of childhood before secondary generalized epilepsy develops and developmental delay and behavioural problems are established. The choice of treatment must be individualized depending on the age and clinical circumstances of the patient and the size and anatomic relationships of the hamartoma (Rosenfeld and Feiz-Erfan, 2007). Although it does not replace conventional surgery, SRS is a good option in selected cases such as highly functioning teenagers and adults where it is important to minimize memory deficit which has a higher chance of occurring following open surgery (Arita et al., 1998; Regis et al., 2004b; Rosenfeld, 2011; Schulze-Bonhage et al., 2004; Selch et al., 2005).

Several studies with different techniques including a gamma source (Gamma Knife, Elekta AG) or LINAC based systems (CyberKnife, Accuray Inc. and Novalis, BrainLab AG) as well as stereotactically implanted iodine-125 seeds, have demonstrated the efficacy of radiation in stopping the spread of epileptic discharges from the hypothalamus to the cortex (Arita et al., 1998; Regis et al., 2004b; Rosenfeld, 2011; Schulze-Bonhage et al., 2004; Selch et al., 2005). The efficacy of SRS for the treatment of hypothalamic hamartomas has been demonstrated to be highly correlated to the delivered dose, with the best results using a marginal dose > 17 Gy and a median prescribed dose of 18%. Post-operative course may be characterized by a short interval (2 months) of epilepsy worsening, followed by a gradual overall improvement (Romanelli et al., 2008; Régis et al., 2007). So far, no major neurological side effects have been reported. The dramatic improvement of sleep quality, behaviour and learning performance in treated children as well as the preliminary observation that younger patients show an excellent outcome with lower doses, should encourage the further investigation of this therapeutic option in controlled trials. Surgical and radiosurgical treatments can be easily integrated in patients harboring large HH. In such cases, a surgical debulking procedure can be followed by radiosurgery delivered to the unresectable epileptogenic intrahypothalamic component. A combined approach can be used to treat large epileptogenic lesions (such as low grade gliomas and arteriovenous malformations) involving eloquent cortex (Friehs et al., 2007). In the authors' experience, microsurgical debulking followed by radiosurgical ablation of the lesional component involving eloquent cortex provides seizure control while minimizing the risk of neurological deficits.

Finally, the combination of non-invasive localization with radiosurgery is an attractive alternative approach to conditions traditionally treated with brain resection. For instance, magnetoencephalography, it has been used to guide low-dose irradiation in refractory seizures arising from eloquent cortical areas (Kurita et al., 2001; Stefan et al., 1998). This approach might become an important approach in the management of mesial-temporal and extratemporal epilepsy, especially if refractory seizures arise from eloquent cortex or surgically challenging regions of brain. Moreover, the outcome of patients treated with SRS should improve as diagnostic techniques for epileptic zone localization, such new MRI sequences and magnetoencephalography continue to evolve.

Multiple subpial transections

The technique of multiple subpial transections (MST) is a surgical procedure originally introduced by Morrell (Morrell et al., 1989) for the management of medically intractable epilepsy with seizure foci in eloquent cortex. MST is generally reserved for patients in which extensive pre-operative and intraoperative neurophysiological evaluation identify epileptogenic cortex arising out of or extending to highly functional brain area, such as primary motor-sensory cortex, language or visual cortex. This technique has been used as an adjunctive approach after microsurgical resection of non-eloquent brain regions, and also alone in severe epilepsy conditions, such as epilepsia partialis continua, Landau—Kleffer syndrome, and Rasmussen encephalitis (Morrell et al., 1995; Molyneux et al., 1998; Irwin et al., 2001; Morell et al., 1991; Morrell and Hanbery, 1969).

The surgical procedure consists of obtaining serial transections of the cortex sparing the white matter, spaced approximately 5 mm apart and oriented perpendicular to the long axis of the selected epileptic gyrus. The rationale for MST is based on the concept that the cerebral cortex is functionally organized in vertically oriented columns of neurons and the transmission of electrical signals, both efferent and afferent, is mostly independent from the horizontal spread of seizure activity (Mountcastle, 1957; Hubel and Wiesel, 1962; Mountcastle, 1997; Chervin et al., 1988). On the other hand, pathological epileptic electrical activity follows a non uniform horizontal spatial pattern, in which the neuronal cell layer V is always involved, sometimes as an epileptic trigger (Telfeian and Connors, 1998; Luders et al., 1981). Thus, the disruption of horizontal cortical interconnections with sparing of vertically oriented fibers will reduce seizure spread, while preserving cortex function. The distance of not less than 5 mm between transections comes from the observation that a minimal contiguity of columns is necessary for function integrity. In addition, the onset of a seizure discharge is continuous at a distance of 4 mm, but it is independent at 6 mm (Morrell et al., 1999). Surgery should avoid the disruption of the pia matter and lesioning sulcal vessels and this is achieved through the use of specially designed epilepsy knives (Mountcastle, 1957). The number of transections are estimated pre-operatively and then refined based upon electrocorticography recordings during the procedure. Therefore, MST can be considered a neuromodulatory technique, as it does not remove the site of epileptogenic activity as with a surgical resection but prevents the development of synchronized pathological ictal discharges in the cortex (Sawhney et al., 1995).

Several retrospective series have been published on MST since its first description but, in most cases, this approach is used in conjunction with surgical resection of a pre-operatively mapped epileptogenic area (Hufnagel et al., 1997; Mulligan et al., 2001; Schramm et al., 2002; Spencer et al., 2002; Orbach et al., 2001; Blount et al., 2004; Shimizu and Maehara, 2000; Asadi-Pooya et al., 2008a). This aspect and the lack of a prospective trial explain the absence of a unanimous opinion on the efficacy of this procedure. As recently reviewed (Blount et al., 2004; Shimizu and Maehara, 2000), it seems that the outcome is better when MST is used in combination with resection surgery rather than alone. Good results have been reported by Spencer et al. (2002) from a metanalysis including 211 patients treated at different centres, concluding that the patient selection is an important variable in predicting outcome. Although less conclusive, due to the limited numbers of patients, results in children seem superior to those of the adult series (Shimizu and Maehara, 2000). Landau—Kleffer syndrome (often children), presents a unique situation because the outcome in this cases is not seizure freedom but rather the improvement in language skills. Variable improvements in speech have been reported, but there are no cases of return to a normal level and the best prognostic factor is length of time from surgery (Irwin et al., 2001). Some MST-related complications are often present due to highly functional activity of the area treated, but can generally be expected to be transient and resolve within one month post-procedure. Another consideration is the late recurrence of seizures recently pointed out by Orbach and colleagues (Orbach et al., 2001), who found a rate of recurrence at 5 years of 18.5%, this is higher than that previously described, especially in those patients without clear neuropathological findings. Overall the long-term data available does not allow strong conclusions to be drawn.

While MSTs require an exquisite localization of the seizure focus because they act by parcellizing and disconnecting the focus itself, disconnective procedures such as callosotomy and hemispherectomy induce seizure palliation by cutting the white matter pathways through which the seizures spread (Asadi-Pooya et al., 2008a; Rahimi et al., 2007). Therefore, these surgical approaches cannot be considered as neuromodulating procedures. The role of anterior two-thirds callosotomy in the treatment of drop attacks is well demonstrated but simple partial, generalized tonic and tonic—clonic as well as myoclonic seizures can also benefit from anterior callosotomy (Tanriverdi et al., 2009; Asadi-Pooya et al., 2008b). Nowadays callosotomy is somehow a second-line treatment after VNS, even for its classical indication, drop attacks (Maehara and Shimizu, 2001). We prefer to offer VNS first, followed by callosotomy if the ensuing seizure control is poor. However, due to the lack of prospective randomized trials, the surgical indication is tailored on a case-by-case basis. Disconnection surgery has also been performed on HH, leading to the reversal of the epileptic encephalopathy without neurological complications (Wait et al., 2011). Finally, hemispherectomy is the most extensive disconnection procedure, practiced in highly selected cases to relieve catastrophic seizures in children with severe or progressive unilateral cortical disease, such as Rasmussen's encephalitis, hemimegalencephaly, Sturge—Weber syndrome, and extensive hemispheric cortical dysplasias. This procedure is associated with substantial morbidity and mortality (Theodore, 2005).

Conclusions

Despite major advances in recent years, epilepsy remains an extraordinary therapeutic challenge.

Nearly one-third of patients with newly diagnosed epilepsy will develop medically refractory epilepsy. Neuromodulation represents an alternative therapy for patients

resistant to drug treatment or who cannot benefit from resective surgery. These techniques have the advantages to directly address the neuroanatomical substrates thought to play a role in seizure generation and propagation and to minimize the potential side-effects of surgical procedures. The ultimate goal of these techniques should be not only to render patients seizure-free, but also to improve the quality of life of individuals and reduce costs of medical care. At this time, VNS therapy has been shown to be efficacious and well tolerated in children and in adults with epilepsy. Notwithstanding the initial cost of the device and implantation, VNS is also a cost-effective treatment, reducing direct medical costs and improving health-related quality of life measures. Moreover, it is the only FDA-approved neurostimulation modality. DBS of various brain regions also appear effective but is not yet approved for clinical use. Preliminary results are encouraging, but not conclusive (De Ribaupierre and Delalande, 2008). Due to the widely studied safety and efficacy, VNS remains today the preferred surgical option for patients unfit to resective microsurgery. A better understanding of the mechanisms of action of brain neuromodulation and future advances in the knowledge of neural circuits that generate seizures and regulate their propagation will hopefully improve the selection of candidates and allow these procedures to be performed more precisely, effectively and safely.

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