Clinical commentary

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The use of electrical source imaging in targeting lesional mesial temporal epilepsy for radiosurgical treatment

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ABSTRACT – Gamma knife radiosurgery (GK-RS) is a technique applied in selected cases of mesial-temporal epilepsy, although still limited to centres with adequate instrumentation and expertise. Here, we report a case of radio surgery targeted with the aid of electrical source imaging that localizes the cortical area generating the scalp epileptic discharges. The patient, a 39-year-old male, presented with a right mesio-temporal lesion; electrical source imaging localization partially overlapped with the lesional area but showed an important activation of the omolateral frontal area, concordant with the epileptic network. The patient underwent GK-RS, with good neurosurgical and clinical results. A radiosurgical ellipsoidal treatment volume area of $2 \times 2 \times 2$ cm^3, located over the right temporo-mesial region within a centre showing abnormal signal intensity, was considered. Seven months after treatment, the patient developed brain oedema that gradually resolved after one year. After three years of follow-up, the patient was seizure-free (Engel class I). Our very preliminary experience suggests that electrical source imaging appears to be a useful supporting tool for the definition of the radiosurgical treatment volume in selected patients with temporo-mesial lesional epilepsy.

Key words: inverse solution problem, epilepsy surgery, radiosurgery, high-density EEG

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Radiosurgery (RS) is a technique that focuses ionizing radiation to small targets deep within the brain, sparing damage to surrounding tissue. It has been used to treat difficult-to-access lesions, such as deep tumours and arteriovenous malformations. The anticonvulsant effects of RS were first observed treating CNS tumours and vascular lesions (Schrottner *et al.*, 1998; Steiner *et al.*, 2010).

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In these cases, however, successful treatment of seizures is almost impossible to distinguish from that of the underlying lesions. Seizure remission rates after RS of arteriovenous malformation range from 55-80% and 25-64% for cavernous malformation (Steiner *et al.*, 2010). The efficacy of RS in treating associated epilepsy was the main factor leading to its use in recent trials of mesial temporal lobe epilepsy (MTLE) (Régis *et al.*, 2004).

The Gamma Knife (GK) Perfexion (Elekta Ab; Stockholm, Sweden) model consists of 192 separate radioactive cobalt-60 sources, housed inside a hemispheric chamber and focused to a single target. The target is determined and maintained with the patient installed into a stereotactic frame on the basis of the neuroradiological data. A complementary localization support may be derived from electrical source imaging (ESI). ESI is an imaging technique for reconstructing electrical activity in the brain from electrical potentials measured on the scalp by solving the associated inverse problem. For epilepsy, it estimates the electric source(s) generating scalp interictal epileptiform discharge (IED) and it is widely used to identify the region to be targeted in surgical treatment (Storti *et al.*, 2013), but has also been applied to study physiological graphoelements, *i.e.* in sleep (Del Felice *et al.*, 2013a; Del Felice *et al.*, 2013b). This approach provides information regarding the localization and propagation in time of the epileptic activity. A high number of electrodes that improve the spatial resolution of surface EEG, combined with precise assumptions of the realistic head models, can enhance its precision. A similar non-invasive approach has been proposed with magnetoencephalography (MEG; 37 channels), with a good concordance of RS target area and dipole localization for extra-temporal lobe foci (Smith *et al.*, 2000). Regarding mesial temporal lobe (MTL) structures, the results reported in the literature are still discordant, possibly due to the sub-optimal scalp-signal detection of MTL electrical activities that decay with distance, and the MTL convoluted anatomy that creates closed electric/magnetic fields (Gavaret *et al.*, 2004; Wennberg *et al.*, 2011).

Here, we report a non-invasive presurgical evaluation, aided by cortical source localization through ESI, to target gamma knife surgery in a patient with lesional MTL epilepsy.

Case study

Patient

The patient was a 39-year-old otherwise healthy male. At the age of 12, the patient began presenting weekly brief episodes of altered self-perception and gastric discomfort, followed by left eyelid myoclonia and dystonic posturing of the arms, more marked on the left. Seizures persisted despite appropriate treatment. Repeated standard EEGs reported right anterio-temporal slowing, intermixed with sharp figures. MRI at age 35 revealed a non-enhancing right mesio-temporal mass, with dysomogenous appearance. A diagnosis of ganglioglioma was proposed, but the patient refused any surgical procedure. Due to persistence of symptoms and lesion enlargement, the patient underwent GK surgery in September 2010. Seven months later, he developed cerebral oedema that subsided after adequate therapy, during which time a simple partial seizure was witnessed. No other seizure was reported afterwards, and three years on, the patient is seizure-free (Engel class I).

High-density EEG acquisition

High-density EEG recording was performed using 256 channels (Electrical Geodesic, Inc., Eugene, OR, USA). The data were recorded against a vertex electrode reference (Cz) at a sampling rate of 250 Hz.

Cortical source imaging reconstruction

High-density EEG data were analysed using Cartool software (http://sites.google.com/site/cartoolcommunity/). The T1-weighted anatomical images were used to create a realistic model of the brain. The solution space for the distributed source model contains 5,014 points uniformly distributed over the grey matter and mapped onto the spherical head model with anatomical constraints (SMAC) (Spinelli *et al.*, 2000). The graphoelement peak was used as trigger for averaging in ±500 ms epochs. A standardized source imaging procedure, low-resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui *et al.*, 1994) constrained to the individual matter, was applied to the averaged spikes. The T1-weighted anatomical MR images were transformed into the MNI coordinate space (FLIRT, FSL toolbox (http://fsl.fmrib.ox.ac.uk) and the region with the maximum value of current density was identified using the Harvard-Oxford Atlas.

Gamma knife targeting and protocol

The radiosurgical technique and protocol have already been described (Nicolato *et al.*, 1997). After the application of the MRI-compatible Leksell Model-G stereotactic frame (Elekta Instruments AB, Stockholm, Sweden) to the patient, 1-T MRI was performed. Three-dimensional dose plans were developed using commercially available software, Leksell Gamma Plan (version 8.3, Elekta Instruments).

We considered, as the radiosurgical ellipsoidal treatment volume, a 3-dimensional area of $2\times2\times2$ cm^3 inside right temporo-mesial region within a centre showing abnormal signal. Optic pathways and mesencephalic area were outlined as eloquent. Prescribed radiation dose of 22 Gy was delivered at 50% of isodose line according to ICRU recommendation criteria (ratio of 1:2 between dose at periphery and maximum dose) with a maximal dose of 44 Gy. The estimation of dose delivered to optic tracts was of 6.6 Gy (risk threshold $<$11 Gy) while 2.5 cc of upper right brain stem received an average of 5 Gy (risk threshold 15 Gy).

GK-RS was performed with Perfexion Leksell Gamma Knife, under local anaesthesia. The patient was discharged from the hospital within 24 hours after treatment, and was clinically and instrumentally (contrast-enhanced MRI) evaluated at six-month intervals.

Results

High-density EEG was recorded pre-surgically during the interictal phase and yielded only short bursts of slow rhythmic activity derived from the right temporal region. The 2D rendering topo-plot located these abnormalities over the frontal and temporal right leads.

The source localization from the beginning of the slow wave to the time point at 50% of the rising phase pointed to bilateral mesial temporal lobes and the right frontal lobe. At peak, electrical activity spread around the rising localization (*figure 1*) to the right frontal area. The maximum of the current density at the peak of the activity was localized to the left inferior frontal gyrus pars opercularis (MNI coordinates: x=141; y=132; z=87).

Neurosurgical results

The patient was seizure-free. The first MRI performed at seven months showed a post-radiosurgical change and no substantial parenchima modifications inside the 22 Gy target area (*figure 2*); brain oedema surrounding peri-lesionally treated target volume in proximity to adjacent mesencephalic eloquent area completely disappeared within one year from GK-RS.

Discussion

In this study, we report GK-RS targeting volume aided by ESI. Targeting is usually performed on the basis of MRI anatomical data. The reconstruction of the cortical generator of scalp graphoelements offers adjunctive information about the epileptogenic zone; ESI depicts the cortical current density distribution, estimating the source time course with a millisecond temporal resolution. Usually, the rising phase of the spike average is associated with the primary focus, whereas the peak of the electrical activity already involves areas of propagation. In our patient, we observed an interesting phenomenon; while the beginning of the electrical activity was associated with a weak electrical activity over the mesial temporal lobes, clinically recognizable as altered self-perception and gastric discomfort reported by the patient, the important spread of electrical activation to the omolateral frontal area

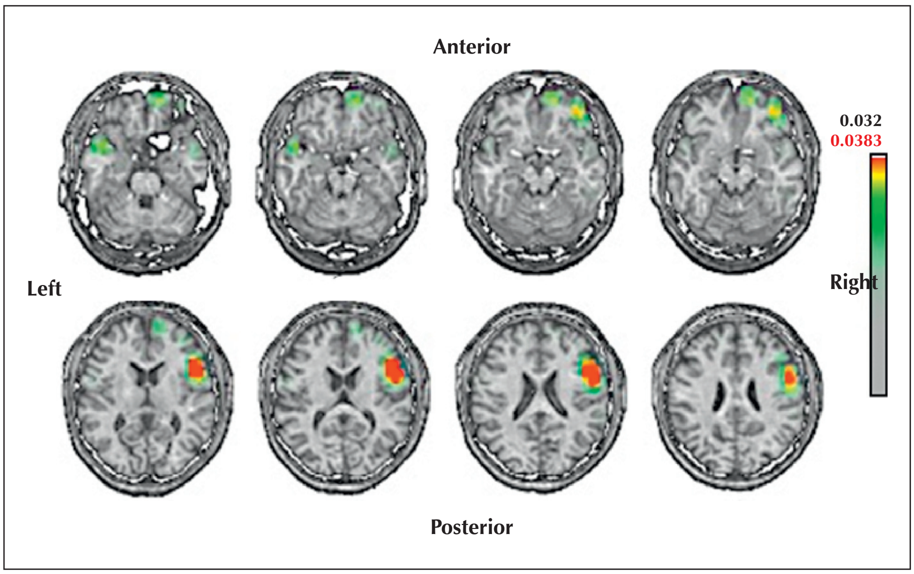

Figure 1. ESI results in MRI native space (source activity at the peak of the spike). The scale indicates the current density (CD) [μA/mm^3].

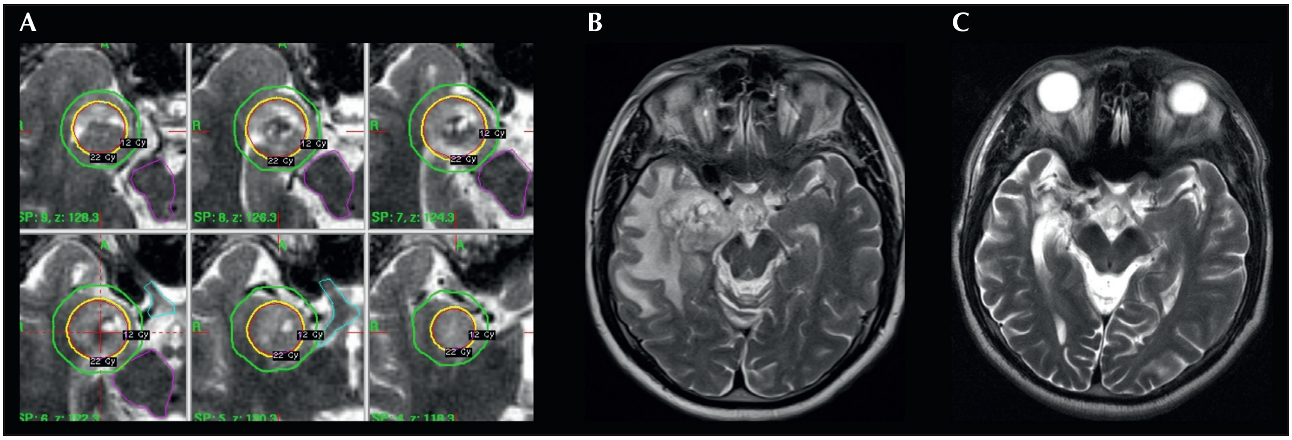

Figure 2. A) MRI on the day of GK-RS, showing the prescription dose lines; B) MRI follow-up at seven months after GK-RS, showing typical post-radiosurgical imaging changes with an important peri-lesional oedema; C) last MRI at 38 months after GK-RS showing a radiosurgical mesial temporal scar, without oedema.

explains the eyelid myoclonia that constituted the dominant feature of the seizure. ESI thus pointed, not only to the epileptogenic zone, but also to the spreading pathways of the pathological activity; severing not only the primary focus but also its connection is an intriguing and promising approach to epilepsy surgery. Several limitations have to be borne in mind. First of all, the source reconstruction is based on a slow scalp activity. The high reliability of source reconstruction has been documented for spikes and is based on the recognition of morphologically identical spikes, whereas other less monomorphic EEG activities, *i.e.* slow waves, have been less frequently adopted (Storti *et al.*, 2013). We are aware of the intense and, as yet, unresolved issue of whether ESI could be a useful tool in MTL epilepsies, mainly due to the scarce surface detection of spikes generated in these deep, convoluted cortices. Indeed, a large pathological mass in this area could generate detectable slow waves, partially overcoming this limitation. Finally, even if the imprecise overlap between ESI maximum and lesion could address this technical problem, an irritative mechanism of ganglioglioma on adjacent tissues is reasonable to explain our finding.

Given the excellent clinical outcome, the epileptogenic mechanism was likely to be severed. Whether this lied in the lesion itself, or was determined by a disruption of the epileptogenic network, cannot be ruled out. To clarify this issue, we propose a systematic presurgical work-up of gamma knife patients with ESI in the context of a multimodal evaluation; shedding light on how epileptogenic mechanisms can be disrupted would also open up new interesting therapeutic options in non-lesional epilepsies.

Conclusion

Our very preliminary experience suggests that electrical source imaging appears to be a useful tool for the definition of the radiosurgical treatment volume in selected patients affected with MTL lesional epilepsy. ☐

Disclosures.
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