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Beyond the lesion: The epileptogenic networks around cavernous angiomas

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Summary The relationship between epileptogenic lesions and the extension of epileptogenicity is a major challenge in presurgical evaluation of drug resistant epilepsies. In this study, we aimed at quantifying the epileptogenic properties of brain structures explored by depth electrodes in patients investigated by stereoelectroencephalography (SEEG) and suffering from focal drug-resistant epilepsy associated with cavernous angioma (CA). Epileptogenicity of the perilesional region and distant brain areas was calculated according to the ''epileptogenicity index'' (EI), a technique that allows mathematical quantification of rapid discharges at seizure onset taking into account the time at which the discharge occurs. Thirteen seizures from 6 patients were studied.

Abbreviations: Am, amygdala; Hip, hippocampus; iTp, internal temporopolar cortex; eTP, external temporopolar cortex; EC, entorhinal cortex; PRh, perirhinal cortex; TBa, anterior temporobasal cortex; TBp, posterior temporobasal cortex; MTGa, anterior part of middle temporal gyrus; MTGp, posterior part of middle temporal gyrus; PHC, parahippocampal cortex; STG, superior temporal gyrus; SMA, supplementary motor area; BA6, premotor lateral cortex; OPF, frontal operculum; OFC, orbitofrontal cortex; PFC(F3), prefrontal cortex, inferior frontal gyrus; PFC (F2), prefrontal cortex, middle frontal gyrus; GC32, cingulate gyrus area 32; CG24, cingulate gyrus area 24; Rol, rolandic cortex superior(s) or inferior (i) parts; FUS, fusiform gyrus; OC, occipital region; Ins, insular cortex; IPL, inferior parietal lobule; pOP, parietal operculum.

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Localization of the cavernoma was the frontal lobe (two cases), the temporal lobe (three cases) or the anterior insula (one case). Visual inspection of the ictal discharge showed that in the majority of cases (5/6) the perilesional region was either not involved or involved with other distant sites. Using EI quantification, complex patterns of epileptogenicity were observed in five patients. A large number of brain regions out of the lesional region disclosed higher values than the lesion site. Mean values in the perilesional region and in the extralesional sites were not significantly different ($p = 0.34$). Complex organization of the epileptogenic zone may be found in drug-resistant CA associated epilepsy. Thus, this result should be borne in mind when patients with CA and drug resistant epilepsy are investigated. If there is a suspicion of a larger epileptogenic zone than the lesion, intra-cerebral exploration by SEEG may be required before surgery that may be guided by the definition of the EZ.

Introduction

Cavernous angiomas (CA) are well-circumscribed, mulberry-like vascular malformations that may be found in the central nervous system in up to 0.5% of the population (Del Curling et al., 1991). CA can be sporadic or inherited. The common symptoms are epilepsy, hemorrhages, focal neurological deficits, and headaches. They represent about 5—20% of all vascular malformations in the central nervous system. Traditionally seizures have been estimated to occur in 40—70% of patients with CA (Chang et al., 2009). However a recent report of a large cohort with long-term follow up (2035 patient-years) showed a rather lower prevalence of seizures at around 30%; these most often occurred without evidence of associated acute hemorrhage (Flemming et al., 2012). Most seizures are focal, without or with secondary generalization and are resistant to antiepileptic drugs in approximately 40% of cases (Chang et al., 2009; Englot et al., 2011; Moran et al., 1999; Ryvlin et al., 1995).

A number of different mechanisms have been proposed to cause epilepsy in patients with cavernomas: mass effect, gliosis, or hemosiderin deposition in the surrounding brain tissue (Chang et al., 2009). These cases with established epilepsy should be distinguished from patients who present only isolated, non-recurring seizures. Surgical resection of the cavernoma and surrounding tissue is often proposed but the surgical strategies in patients with CA are still unclear (Fernandez et al., 2012; von der Brelie and Schramm, 2011). A large proportion of surgical reports deal with heterogeneous case series, which include patients with various epileptological contexts, ranging from sporadic episodic seizures to drug resistant epilepsy (Englot et al., 2011; von der Brelie and Schramm, 2011). Since the etiology and prognosis are likely to be quite different for these two ends of the spectrum, global evaluation of outcome is rather difficult.

The rate of success is therefore variable in the literature as recent review has well pointed out (Englot et al., 2011). In most of the cases, surgical strategy is decided on neuroimaging data sometimes completed by non-invasive video EEG recordings. The causes of the failure (occurring in 30—70% of cases) are not well explained. Removal of the hemosiderin ring surrounding the lesion may improve outcome but remains debated (Hugelshofer et al., 2011). Use of elecrocorticography to define seizure onset zone, with resection extending beyond the cavernoma and its hemosiderin ring if necessary, has been associated with better outcome (Van Gompel et al., 2009). A shorter preoperative history of epilepsy ($\leq$1 year) was also found to be an important factor of therapeutic response in recent meta-analysis (Englot et al., 2011).

Extension of the epileptogenic zone out of the lesional site could be another explanation for poorer outcome that has been however rarely addressed. The fact that widespread networks may be observed in cases of focal epileptogenic lesion has been demonstrated in focal cortical dysplasia or dysembryoplastic tumors (Aubert et al., 2009; Chassoux et al., 2012a, 2012b) and is a probable important prognostic factor after epilepsy surgery.

To the best of our knowledge, there is no detailed intracerebral EEG study of the epileptogenic zone (EZ) in CA.

In this study, we thus aimed at quantifying the epileptogenic properties of brain structures explored by depth electrodes in patients investigated by stereoelectroencephalography (SEEG) and suffering from focal drug-resistant epilepsy associated with CA. This quantification was performed using the epileptogenicity index (EI). We determined EI from signals recorded in distinct brain structures including the perilesional region.

Patients and methods

Patients and SEEG recordings

Patients suffering from drug-resistant focal epilepsies associated with cavernomas and who had undergone intracerebral recording (stereoelectroencephalography, SEEG) were included in the study.

They were selected from a retrospective analysis of 295 patients in our epilepsy center database and investigated with SEEG during presurgical evaluation for drug resistant epilepsy between 2000 and 2012. Six patients required invasive recordings after the non-invasive phase for their epilepsy associated with CA. SEEG was indicated because the epileptogenic zone was suspected to be larger/or discordant regarding the lesion localization or because of the localization in or close to eloquent cortex.

SEEG recordings were done according to previous reports (McGonigal et al., 2008; Talairach et al., 1992). The placement of electrodes was based upon available non-invasive information providing hypotheses about the localization of the epileptogenic zone. Therefore, the number of electrodes and their location were defined for each individual

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