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Clinical topography relationship in patients with parenchymal neurocysticercosis and seizures

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ABSTRACT

Objective: Discordances between imaging findings of parenchymal neurocysticercosis and seizure expression have been reported, and as such the possibility that neurocysticercosis and seizures may frequently coexist by chance has been raised. In this study, we evaluate the topographic relationship between seizure foci based on semiology and electroencephalography with the location of parenchymal neurocysticercotic lesions.

Methods: Seizure information, neuroimaging (computed tomography and magnetic resonance imaging [MRI]) and electroencephalographic data from three randomized clinical trials of individuals with parenchymal neurocysticercosis and focal seizures were analyzed. Blinded epileptologists defined a potential seizure onset zone and a symptomatogenic zone for each individual based on semiology. The topographic relationship between semiology, either lesion location or areas of perilesional edema on baseline MRI, and electroencephalographic abnormalities were assessed.

Results: Fifty-eight patients with one or two parenchymal neurocysticercotic lesions were included in this study. From them, 50 patients (86%; 95% CI, 75%–93%) showed a clinical-topography relationship with the potential seizure onset zone, and 44 (76%) also with the symptomatogenic zone. From the eight patients with no topographic relationship, five had focal seizures 30 days before or after the baseline MRI and showed perilesional edema. All of these five patients showed a clinical-topography relationship between such seizures and an area of perilesional edema, making a total of 55 patients (95%; 95% CI, 85%–99%) with clinical-topography relationship when perilesional edema is considered. Most patients with focal epileptiform discharges (7/8, 88%) had a topographic association between electroencephalographic focality, the potential seizure onset zone and a cysticercotic lesion.

Conclusion: Seizure semiology and focal epileptiform discharges are topographically related to neurocysticercotic lesions in most patients. These data strongly support seizure origin in the cortex surrounding these lesions.

1. Introduction

Neurocysticercosis (NCC), a helminthic infection of the central nervous system caused by the cystic larval stage of the pork tapeworm *Taenia solium*, is the leading cause of epilepsy in most resource-poor countries (Garcia et al., 2014c; Singh et al., 2013). Neurocysticercosis is

Abbreviations: AED, antiepileptic drug; APT, antiparasitic treatment; CI, confidence interval; CT, computed tomography; EEG, electroencephalography; EITB, enzyme-linked immunoelectrotransfer blot; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; MRI, magnetic resonance imaging; NCC, neurocysticercosis; SD, standard deviation

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a common infection in endemic regions (Moyano et al., 2016), and in field conditions between 10 and 20% of the general population may show NCC lesions in neuroimaging examinations (Montano et al., 2005; Moyano et al., 2016). Only a minority of these individuals, however, would have a history of seizures (Moyano et al., 2016; Prasad et al., 2011).

There are discordances between imaging findings of NCC and seizure expression, both in field studies and in clinical cases (Del Brutto et al., 1992; Duque and Burneo, 2017). In a community-based MRI survey, there was no difference in proportions of patients with seizures regarding number, stage or location of cysticercotic lesion (Prasad et al., 2008). In another study, seizure frequency was not related to the burden of cysticercotic lesions (Kowacs et al., 2006). On the basis of these observations, the possibility that NCC and seizures may frequently coexist by chance has been raised (Kowacs et al., 2006; Prasad et al., 2008; Saito et al., 2016; Sakamoto et al., 1999).

Only a few studies have assessed the topographic relationship between seizure semiology or electroencephalographic (EEG) findings and cysticercotic lesions (Cukiert et al., 1994; Murthy and Reddy, 1998; Singh et al., 2000). Such association was observed in only half of cases. These studies, however, had serious limitations. They were performed with old-fashioned computed tomography (CT) equipment only or were based on anatomical divisions in brain lobes.

Seizure semiology is an extremely valuable tool to assess patients with epilepsy (Tufenkjian and Luders, 2012). In patients with a presumable epileptogenic lesion, semiology plus EEG might accurately determine whether the given lesion is responsible for the observed seizures. More-constrained functional areas in relation to epilepsy are now helping to identify more efficiently the seizure origin (Bonini et al., 2014; Tufenkjian and Luders, 2012). In this study, we took advantage of three historical cohorts of patients with NCC to evaluate the topographic relationship between seizure foci based on semiology and EEG with the location of cysticercotic lesions assessed with magnetic resonance imaging (MRI) and CT.

2. Materials and methods

Individuals with parenchymal NCC and focal seizures (based on semiology) from three clinical trials (Garcia et al., 2014a, b; Garcia et al., 2016) were selected in order to evaluate whether their seizures and EEG focality were topographically related to NCC lesions. To reduce the likelihood of falsely finding a relationship by chance, we selected patients with only one or two cysticercotic lesions of any stage (viable, degenerating or calcified cysts) located juxtacortically (either in the cortex or in the cortical-subcortical junction).

For topographic purposes, we divided each brain hemisphere in 21 functional areas related to epilepsy (Table 1) (Luders, 2008). For each patient, the areas that could have elicited his/her initial seizure manifestations by local activation or seizure spread were termed *potential (suspected) seizure onset zone*, and the areas that probably produced the initial manifestations through only local activation were defined as *symptomatogenic zone* (Rosenow and Luders, 2001). Both zones were defined based on semiology, and hence, from this perspective, a potential seizure onset often included more functional areas than a symptomatogenic zone. For each patient, blinded epileptologists determined both zones and read EEG recordings.

2.1. Study population and data collection

Data was collected from three already published clinical trials assessing antiparasitic treatment (APT) for viable NCC (Garcia et al., 2014a, b; Garcia et al., 2016). Participants had been recruited from four tertiary-care hospitals in Lima, Peru and followed between April 2006 and October 2013. Common to the original trials, inclusion criteria were age between 16 and 65 years, at least one viable cysticercotic cyst, serological confirmation on enzyme-linked inmmunoelectrotransfer blot assay (EITB, western blot) and at least one seizure in the previous year but a seizure history not longer than 10 years. No patient was receiving APT at the period of enrolment, but it was offered weeks after enrolment as the purpose of the clinical trials. At enrolment, neurologists obtained detailed medical histories from the patients and all available eyewitnesses, and recommended patients to take antiepileptic drugs (AED) regularly during the whole follow-up. Baseline EEG, MRI and CT of the brain were performed. Follow-up lasted at least one year with active seizure surveillance (Garcia et al., 2014a, b; Garcia et al., 2016). Patients were instructed to recognize events suspected of being a seizure, to register them in a seizure control diary and to immediately report to the study team. The study neurologist interviewed the patient and available eyewitnesses in the day of the event or the following days to determine whether the event was a seizure. Some seizures were witnessed during hospitalization. Parent trials were approved by the main Institutional Review Board (IRB) of the Universidad Peruana Cayetano Heredia and included permission for further use of the data. A separate IRB approval was obtained for this analysis.

Table 1
Functional brain areas related to epilepsy.[a]
(modified from Luders, 2008).

Lobe or region	Functional brain areas
Perirolandic region[b]	Lateral perirolandic Mesial perirolandic
Frontal lobe[c]	Premotor Negative motor/Broca's language[d] Dorso-lateral frontal Frontal pole Orbitofrontal Supplementary motor Pre-supplementary motor Mesial prefrontal Anterior cingulate gyrus
Parietal lobe[e]	Postero-superior parietal cortex Postero-inferior parietal cortex Precuneus Posterior cingulate gyrus
Temporal lobe	Mesial Neocortical
Occipital lobe	Primary visual cortex Secondary visual cortex
Insular lobe	Anterior insula Posterior insula

[a] Functional brain areas, for each hemisphere, considered as exclusive categories.
[b] Includes the primary motor and primary somatosensory cortex.
[c] Excludes the primary motor cortex.
[d] Broca's language area was considered as present only in the dominant hemisphere where overlaps with the negative motor area.
[e] Excludes the primary somatosensory cortex.

2.2. Seizure evaluation and semiology-based zones

Two epileptologists (A.L.E. and W.Z), blinded to neuroimaging and EEG, revised all descriptions of paroxysmal events to confirm those consistent with seizures, and registered all seizure descriptions using standard semiological terminology (Blume et al., 2001; Fisher et al., 2017; Luders et al., 1998). Focal seizures may evolve or not to bilateral tonic-clonic seizures. First, epileptologists independently localized and lateralized potential seizure onset and symptomatogenic zones for seizures occurred before APT onset, and separately, for seizures that occurred after APT. Additionally, both semiology-based zones were localized considering only seizures occurred 30 days before or after the baseline MRI, but prior to APT. Finally, both zones were determined for each patient using all seizures occurred before enrolment and during