Clinical commentary

Epileptic Disord 2020; 22 (4): 506-10

Neurocysticercosis and pharmacoresistant epilepsy: possible role of calcified lesions in epileptogenesis

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Received September 23, 2019; Accepted April 5, 2020

ABSTRACT – Neurocysticercosis is a neglected and usually poverty-related disease of high public importance. The mechanisms by which the calcified lesions cause epilepsy are not known, but have been attributed to residual perilesional gliosis or an inflammatory process. This case shows that an inflammatory response to a calcified granuloma may be associated with the development of epilepsy. The increase in glutamate and kinin B1 (pro-epileptogenic) receptors added by reduced expression of kinin B2 (anti-epileptogenic) receptors may explain the chronic epileptogenesis associated with the lesion, corroborating the hypothesis of inflammatory mechanisms involved in the pathophysiology of epilepsy in these patients.

Key words: *Taenia solium*, immunohistochemistry, inflammatory markers, seizures

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Neurocysticercosis (NCC), associated with the larval phase of *Taenia solium* in the human central nervous system (CNS), is a neglected and usually poverty-related disease of high public importance (Coyle *et al*., 2012).

Acute symptomatic seizures may result from transitional or degenerating parasites as a consequence of the acute inflammatory response (Carpio and Romo, 2014). Seizures may also occur as a result of infarcts related to vasculitis and thrombosis of penetrating vessels from subarachnoid cysticercosis (Del Brutto, 1992). Encephalomalacia and gliosis, resulting from prior

doi:10.1684/epd.2020.1188

inflammation, accompanies the formation of granulomas with or without calcification and are potential causes of persistent seizure activity (Rathore *et al*., 2013).

In the chronic phase, seizures require treatment with antiseizure medication and some may progress to refractoriness to treatment (Carpio and Romo, 2015); the seizures are the basis for the diagnosis of epilepsy with inflammatory/structural aetiology.

In the specific setting of a residual calcified lesion, associated epilepsy was previously considered to be related to a remote aetiology, once the non-inflamed calcified cysts were regarded as inert (Sotelo *et al*., 1985). However, studies support the existence of a subset of calcified lesions that could be the source of intermittent ictal activity and of a chronic inflammatory process, often associated with the temporary presence of perilesional oedema (Nash and Patronas, 1999). Regarding this topic, only a few examples of the histopathology of calcifications are described in the literature (Gupta *et al*., 2002; Robinson *et al*., 2012).

This study aimed to measure the cellular expression of immunohistochemical (IHC) markers of epileptogenesis in a single calcified cysticercus in a girl with refractory epilepsy which started at three years old; the patient has been seizure-free for 25 months following lesionectomy.

Case study

A six-year-old, right-handed female presented with seizures that started at three years of age, with a frequency of 3 to 30/day. She presented with myoclonic seizures and brief behavioural arrest without automatisms or post-ictal symptoms, leading to an initial hypothesis of generalized epilepsy. She had been on multiple antiseizure medications, including maximally tolerated doses of levetiracetam, valproate, ethosuximide, topiramate, and cannabidiol, in addition to a ketogenic diet, on admission to our tertiary service. The patient had no neurological deficits, and her intellectual level was within the lower middle range. Long-term video-EEG monitoring showed numerous myoclonic-tonic, asymmetric tonic, and behavioural arrest seizures. The EEG also showed epileptiform activity in the right frontal region, with secondary bilateral synchrony (*figure 1B*). Ictal EEG revealed frontal onset seizures. Brain MRI showed a nodular calcification located in the right mid-frontal gyrus, depicted by marked hypointensity on all sequences, including susceptibility weighted imaging, surrounded by hyperintensity on T2 and FLAIR (*figure 1A*). After failure of treatments with carbamazepine and clobazam, the patient underwent a multidisciplinary evaluation followed by a resection of the calcified lesion. Because the lesion was close to the motor area, the initial surgical planning included intraoperative mapping of the hand motor area and acute electrocorticography. However, this delimitation was not possible intraoperatively, despite the use of different stimulation parameters. A long-term study with subdural electrodes was then performed, allowing the delineation of the irritative and ictal onset zones, as well as localization relative to the hand motor area. Histopathological analysis showed a cysticercus with necrosis, a regressive phenomenon of the vesicle wall, of which the scolex was surrounded by a non-specific chronic inflammatory process (*figure 1C*).

Postoperatively, the patient did not present any deficits and has been seizure-free for 25 months since surgery; in addition, her neurocognitive profile was maintained. The resected tissue was submitted for immunohistochemical study in order to evaluate the presence of neurotransmitters and inflammatory markers (*figure 2*).

Discussion

This case illustrates a focal frontal epilepsy with seizure semiology and EEG findings leading to an initial erroneous diagnosis of generalized epilepsy, with absences and myoclonic seizures. Myoclonia was recognized as possibly generalized or focal based only on the most recent classification of seizures (Fisher *et al*., 2017). Additionally, the EEG of this patient, with very frequent bilateral synchrony and rare focal frontal sharp waves, further complicated the analysis.

The epileptogenic potential of a calcified cysticercus requires further clarification. Calcified lesions are common in asymptomatic individuals, and studies report that these lesions are mainly incidental, which questions their true epileptogenicity (Leite *et al*., 2000). Besides being considered inert for a long time (Sotelo *et al*., 1985), recent studies suggest that calcifications of NCC may cause seizures when parasitic antigens retained in the calcium matrix are exposed to the immune system, inducing a recurrent inflammatory reaction (Nash *et al*., 2008). However, it is not clear whether the perilesional oedema frequently seen in NCC patients is the cause or the consequence of seizures (Leite *et al*., 2000), representing an inflammatory reaction or merely postictal vasogenic oedema (Nash and Patronas, 1999; Nash *et al*., 2008). In addition, the perilesional gliosis, as observed in this patient, has been considered to be suggestive of epileptogenic potential (Rathore *et al*., 2013).

The multifactorial concept of epilepsy is based on the triad of epileptogenic abnormality, seizure threshold, and precipitating factors (Engel *et al*., 2013). In the context of NCC, the epileptogenic abnormality relates to

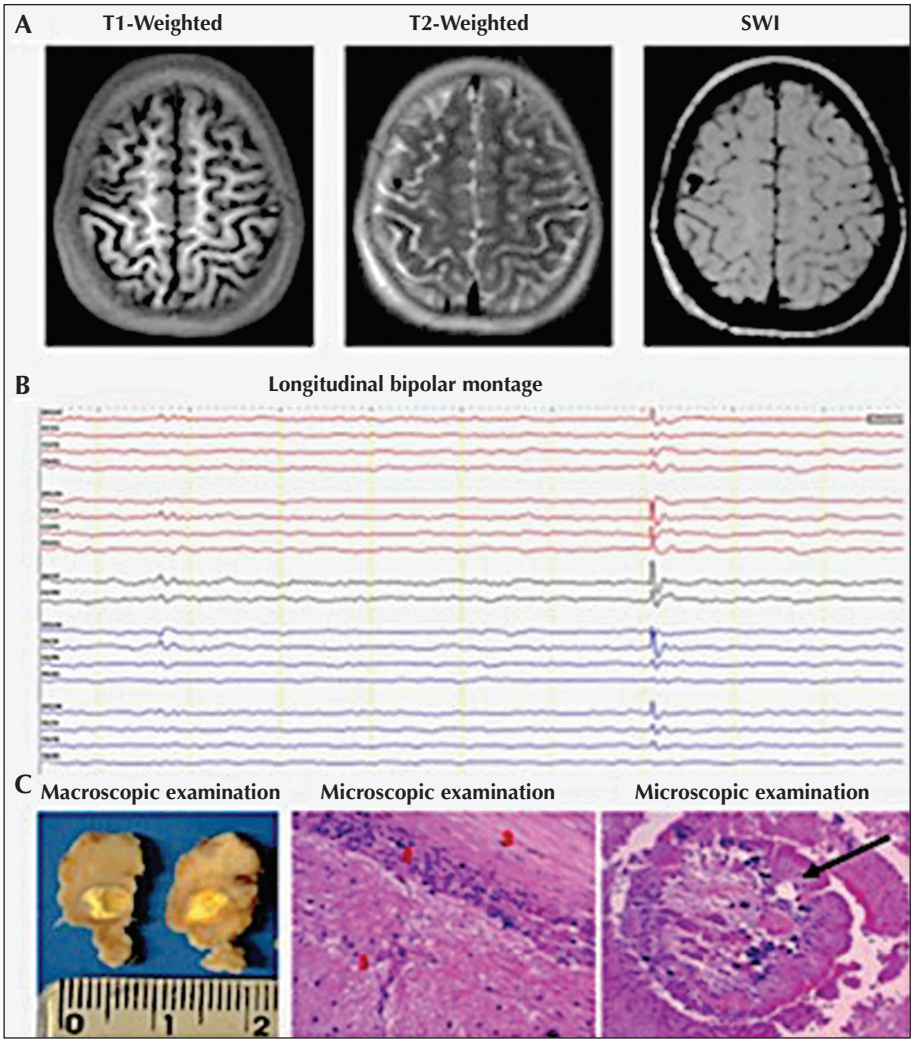

Figure 1. Diagnostic assessment for seizure localization and neuropathology. (A) Representative slices of 3T brain MRI with T1, T2-weighted and susceptibility-weighted image (SWI) sequences showing calcification located in the right mid-frontal gyrus. (B) Scalp EEG with longitudinal bipolar montage. (C) Left panel: macroscopic examination showing a calcified cysticercus resected from the middle frontal gyrus; middle panel: microscopic examination of samples stained with haematoxylin-eosin showing a calcified cysticercus with inflammatory cells and astrocytic gliosis (1: cerebral cortex with astrocytic gliosis; 2: lymphocyte cells; 3: fibrosis wall); right panel: scolex fragments (arrow) surrounded by a non-specific chronic inflammatory process.

the number and localization of parasites, as well as their evolutionary phases over time. Additionally, a genetic predisposition might be responsible for a low seizure threshold hastened by precipitating factors such as the host immunologic response, with a cascade of events such as blood-brain barrier breakdown, brain inflammation, and reactive astrogliosis. The biomarkers (the increase in glutamate and pro-epileptogenic kinin B1 receptors) reported in this clinical case would correspond to the "precipitating factors". The effect of all these factors would lead to the chronic epileptogenic process (Carpio and Romo, 2015).

A basic assumption links the pathogenesis of epilepsy and the generation of synchronized neuronal activity with an imbalance between inhibitory GABA-mediated and excitatory glutamate-mediated neurotransmission, which favours the latter. In this study, IHC staining for neurotransmitters and inflammatory markers showed increased levels of glutamate and its transporters around the lesion relative to more distant tissue; the opposite was seen for the expression of GABA markers (*figure 2B*).

One study showed that the activated microglia releases proinflammatory cytokines, which may lead to neuronal hyperexcitability and neurodegeneration. The microglial and astrocytic activation likely contributes to the epileptogenesis (Benson *et al.*, 2015). In this case, immunofluorescence analysis of Iba1 (a specific calcium-binding protein for microglia/macrophage) showed a decreasing gradient

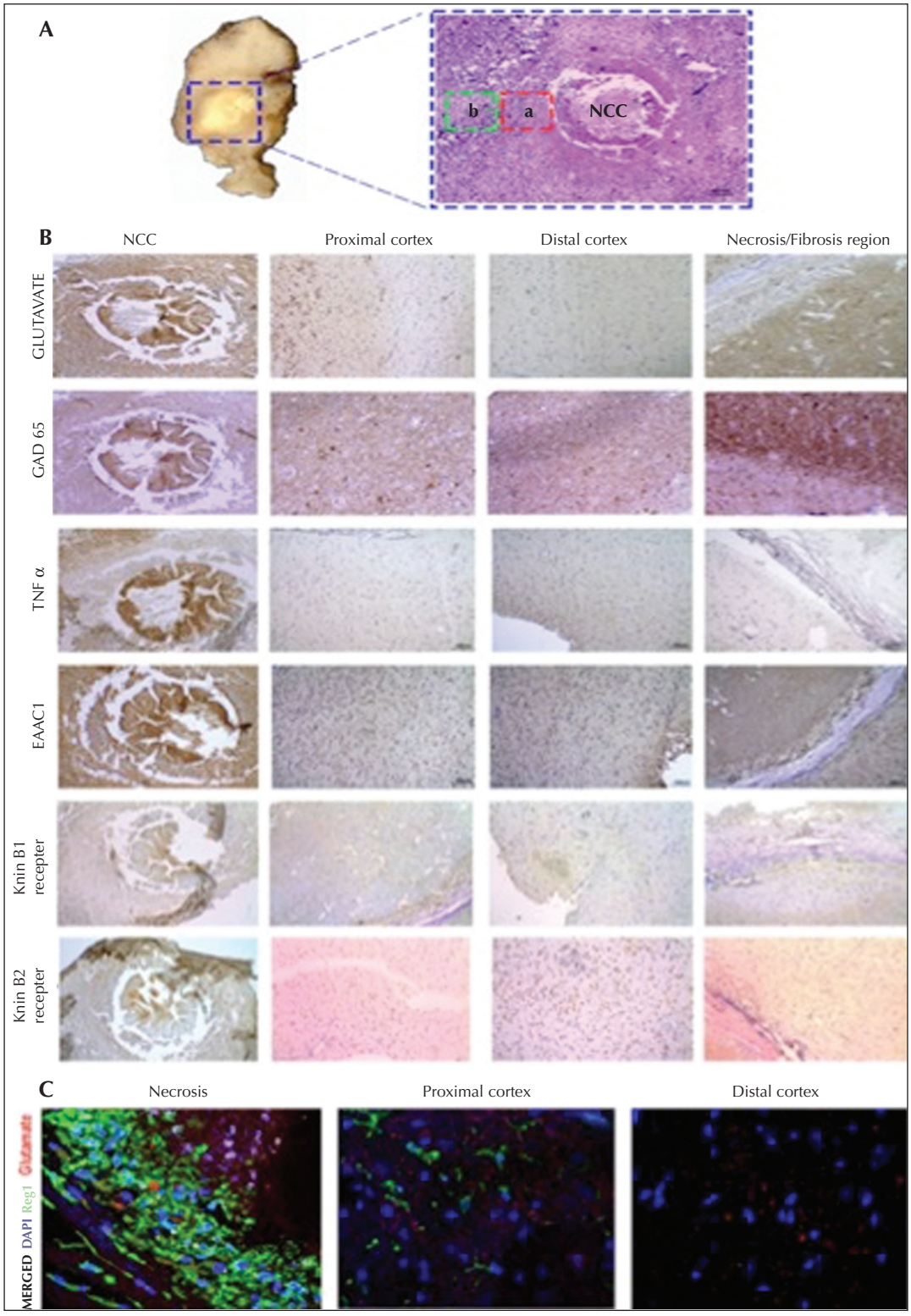

Figure 2. Neuropathological and immunohistochemical analysis. (A) Fragment of brain tissue containing the calcified granuloma. An amplified image shows cresyl-violet staining of the lesion. Insets, *a* and *b*, represent proximal (up to 200 μm from the NCC fibrous wall) and distal (more than 200 μm from the NCC fibrous wall) cortex regions, respectively, for which the IHC analysis was performed. (B) Evaluation of immunohistochemical markers in representative slices from different regions (left panel: x5 magnification; other panels: x10 magnification). (C) Immunofluorescence (magnification: x40); note the marked increase in microglial activation in the necrotic and proximal regions.

of microglia density from the proximal to the distal cortex. The necrotic areas presented the highest concentration of microglia.

Furthermore, the kinin B1 receptor, weakly expressed under physiological conditions, is induced by injury or upon *in vivo* or *in vitro* exposure to pro-inflammatory mediators. The kinin B2 receptor subtype, on the other hand, is constitutively and widely expressed throughout the central and peripheral nervous system (Arganaraz *et al*., 2004). Accordingly, in this case, the increased B1 receptor, as a marker of kinins in the cysticercus and around the lesion, relative to B2 receptor, was suggestive of epileptogenic properties.

This case shows that the inflammatory response due to a calcified granuloma might be associated with the development of seizures and epilepsy. The increase of glutamate and pro-epileptogenic B1 receptors in proximal cortex associated with a reduction of GABA and anti-epileptogenic B2 receptors are findings that might explain the chronic epileptogenesis of the lesion, corroborating the hypothesis of neurotoxicity and inflammatory mechanisms involved in the pathophysiology of epilepsy in patients with neurocysticercosis. A calcified cysticercus can be a cause of epilepsy refractory to medication and should be considered for surgical treatment with a potential chance of cure when the epileptogenic lesion is removed. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgments and disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Could a calcified cysticercus alone be responsible for focal refractory epilepsy?

(2) Are myoclonic seizures always generalized?

(3) What is the possible mechanism responsible for seizure generation due to a calcified cysticercus?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".