Letter to the Editor

Migrainous headaches, calcified cysticercosis and breakthrough seizures

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Keywords
breakthrough seizures, calcifications, cysticercosis, headache, migraine, neurocysticercosis

Date received: 19 October 2021; Received revised November 23, 2021; accepted: 8 January 2022

To the Editor,

Neurocysticercosis is the infection of the central nervous system and its coverings by the larval stage (cysticercus) of Taenia solium, the pork tapeworm. Parasites may lodge in brain parenchyma, subarachnoid space, ventricular system or spinal cord, causing a myriad of pathological changes that are responsible for the clinical pleomorphism of this disease. While epilepsy is the most common clinical presentation of neurocysticercosis, more than one-third of patients present with headache as the single or most important manifestation of the disease.1

Neurocysticercosis-related headaches have been mostly associated with intracranial hypertension related to either hydrocephalus, giant extraparenchymal cysts, or cysticercotic encephalitis. These forms of neurocysticercosis clearly represent the minority of cases. Most patients with calcified cysticerci in the brain parenchyma develop headache without the presence of any additional evidence of intracranial hypertension or focal neurological deficits.

Mechanisms involved in the association between headache and parenchymal brain calcified cysticerci are elusive. A door-to-door epidemiological survey conducted in a community where cysticercosis is endemic, disclosed that 19 out of 57 (33%) migrainous individuals receiving head CT had calcified cysticercosis.2 In addition, a case-control study nested to a population-based cohort disclosed that lifetime headache prevalence, current headaches, intense headaches and, in particular, migrainous (but not tension-type) headaches, were almost five times more frequent among patients with calcified neurocysticercosis than in their matched controls without neurocysticercosis.3 These studies provide grounds for the further evaluation of the association between headache and calcified neurocysticercosis, particularly with the aim to better understand pathogenetic mechanisms involved in its occurrence and potential therapeutic interventions. The pathogenesis of migrainous headaches related to calcified cysticerci is not completely understood. Calcifications represent the end stage of previously viable cysticerci that have been destroyed by either the host immune system or as the result of cysticidal drug therapy. Calcified cysticerci have been considered inert lesions. However, recent evidence strongly suggest that these lesions contain trapped antigenic parasitic membranes, which may be intermittently presented to the host immune system when structural changes in the calcifications related to remodeling mechanisms allow antigenic remnants to be in contact with neighboring cerebral tissues.4 This exposure induces inflammatory changes in the brain parenchyma with the subsequent breakdown in the blood-brain barrier, edema formation and oxidative stress resulting from liberation of nitric oxide and other free radicals. These events may be the pathogenetic substrate for the occurrence of seizures, which often take the form of breakthrough seizures, since they ensue unexpectedly after a seizure-free interval and occur despite the regular use of antiseizure medications.5

In addition, the above-mentioned oxidative stress upregulates the liberation of the calcitonin gene-related peptide (CGRP) by perivascular sensory fibers, which is a key

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effector molecule in migraine that stimulates the trigemino-vascular reflex, thus causing a migraine attack. In addition, it has also been shown that CGRP downregulates the expression of the enzyme nicotinamide adenine dinucleotide phosphate oxidase and increases the activity of antioxidant enzymes. These by-products may reduce inflammation and stabilize the blood-brain barrier, thus controlling neurogenic inflammation. Therefore, mechanisms triggering a migraine attack may be, at the same time, protective for the occurrence of breakthrough seizures (Figure 1).

A longitudinal prospective study, conducted in a cysticercosis-endemic region, will allow characterization of the above-mentioned premises, namely, is there a protective effect of migrainous headaches in the occurrence of breakthrough seizures in patients with calcified cysticerci? And, if so, is there a role of CGRP in this setting? In such study, acute migrainous attacks and breakthrough seizures should be monitored with repeated neuroimaging exams to compare if changes, in particular perilesional edema and abnormal enhancement surrounding previously inert calcifications, are similar across subjects who experience a migrainous attack than in those who develop breakthrough seizures.

Individuals with calcified parenchymal brain cysticerci should be followed to assess whether those who present frequent migrainous headaches are less prone to develop breakthrough seizures or if the latter do not occur in temporal relationship with headache episodes. A close monitoring of the study population would be of value for systematic measurement of salivary CGRP-like immunoreactivity levels using western blotting based technology during acute migrainous attacks and breakthrough seizures. Using this reliable assay, it would be possible to demonstrate if migrainous attacks in patients with calcified neurocysticercosis are CGRP-dependent and whether this peptide is inversely associated with the occurrence of breakthrough seizures.

CGRP monoclonal antibodies are increasingly used for migraine prevention with promising results. If the hypothesized protective effect of CGRP expression on breakthrough seizures is demonstrated, this may have important therapeutic implications since these drugs should be avoided in patients with neurocysticercosis-related migrainous headaches.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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