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Single parenchymal brain cysticercus. Relationship between age of patients and evolutive stage of parasites

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Abstract

Background—A recent hypothesis suggested that in many cases cysticercal granulomas represent recently established *Taenia solium* metacestodes rapidly destroyed by the host's immune system. Here, we attempted to determine whether patients with cysticercal granulomas are younger than those with other forms of parenchymal brain cysticercosis.

Methods—Series of 185 patients with single parenchymal brain cysticercus, classified according to the stage of the parasite at the moment of diagnosis in cysts without inflammation, cysts with inflammation, granular lesions, and calcifications. We correlated the age of the patients with the parasite evolutive stage.

Results—Patients with cysticercus granulomas were significantly younger than those with vesicular cysts (17.7 ± 12.9 versus 36.8 ± 15.1 years, $p < 0.005$) or calcifications (17.7 ± 12.9 versus 40.8 ± 19.7 years, $p < 0.0001$). There was also a non-significant trend for patients with granulomas to be younger than those with colloidal cysts (17.7 ± 12.9 versus 26.7 ± 15.6 years, $p = 0.367$).

Conclusions—Results from this study argued against the classical hypothesis that granulomas are the end result from long-established vesicular cysts destroyed by the host's immune system. Vesicular (viable) cysticerci must be treated with cysticidal drugs as it is unlikely that they will be spontaneously destroyed.

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Introduction

Cysticercosis occurs when humans become intermediate hosts of the tapeworm *Taenia solium*. Parasites have a tendency to invade the nervous system, where they may lodge in brain parenchyma, subarachnoid space, ventricular system, or spinal cord. The former is the most common form of presentation of neurocysticercosis and a leading cause of acquired epilepsy worldwide [1].

There has been much debate on the natural history of parenchymal brain cysticerci, a controversy that has had important therapeutic implications. Indeed, thousands of patients might have been deprived from specific therapy on the incorrect assumption that most parenchymal brain cysticerci will be soon destroyed by the host immune system without the need of cysticidal drugs [2]. This concept probably originated from classical pathological studies suggesting that when *Taenia solium* metacestodes enter the nervous system, they first establish as vesicular (viable) cysticerci. Then, vesicular cysts will remain viable until they experience—as the result of the host's immune attack—degenerative changes that end with the transformation of the parasite into a calcified nodule. Intermediate evolutive stages during which cysticerci experience such degenerative changes have been called “colloidal” (cysticerci showing degenerative signs but still with liquid contents) and “granular” (compact lesions with more advanced degenerative changes) stages, respectively [3].

An alternative hypothesis recently proposed that in many cases cysticercal granulomas are not the result of degenerated vesicular cyst that had been living for years in the brain parenchyma (going first through the vesicular and the colloidal stages, respectively), but represent early or recently established metacestodes rapidly detected and destroyed by the host's immune system, in which the transition through the vesicular and the colloidal stages occurred in a very short time or did not occur at all [4]. This hypothesis is supported by the higher prevalence of a single cysticercus granuloma in populations who are exposed to low parasite loads, and the low sensitivity of serological assays in patients with a single cysticercus granuloma. In addition, a pilot study comparing the age of patients with single cysticercal granuloma versus that of those with single vesicular cyst, showed that the former were slightly younger [4]. This finding argued against considering cysticercal granuloma as the result of the degeneration of vesicular cysts. We studied a series of patients with single parenchymal brain cysticerci in different evolutive stages, to support the hypothesis that cysticercal granulomas are not always the result of degeneration of vesicular cysts that had been living for years within the brain parenchyma.

Methods

From a total of 331 consecutive patients with neurocysticercosis evaluated by one of us (O.H.D.) from January 1990 to December 2009 at a single center (Hospital-Clínica Kennedy, Guayaquil), we selected all the 185 patients with CT evidence of a single parenchymal brain cysticercus who had not received cysticidal drugs prior to their first visit to the clinic. There were no exclusions based on symptoms or age. Patients were classified according to the stage of the parasite at the moment of diagnosis in four groups: 1) cysts without inflammation, 2) cysts with inflammation, 3) granular lesions, and 4) calcifications.

As described elsewhere, each of these evolutive stages of parenchymal brain cysticercus present with characteristic neuroimaging findings that allow their characterization [5]. Then, we correlated the age of the patients with the evolutive stage of the parasite to evaluate if there was any relationship between these variables. The Kruskal Wallis test was used to assess the significance of the difference between the variables analyzed. Differences were considered significant if $p < 0.05$. Statistical analysis of data was carried out using SPSS10 software (SPSS Inc., Chicago, Illinois, USA).

Results

The 185 patients were 79 men and 106 women, with a mean age of 34.9 ± 19.6 years. One-hundred nine patients (59%) had a single parenchymal brain calcification, 35 (19%) had a cyst with inflammation (coloidal cyst), 23 (12%) had a cysticercus granuloma, and the remaining 18 (10%) had a cyst without inflammation (vesicular cyst). Mean age of patients according to the evolutive stages of parasites were: cysticercus granulomas 17.7 ± 12.9 years, colloidal cysts 26.7 ± 15.6 years, vesicular cysts 36.8 ± 15.1 years, calcifications 40.8 ± 19.7 years (Figure 1).

When comparing the age of the patients according to the evolutive stage of the parasites—using the Kruskal Wallis test—we found a significant difference in the age of patients across the four different evolutive stages of parasites ($\chi^2=35.88$, $p < 0.001$). Using post-hoc tests, we found that patients with a cysticercus granuloma were significantly younger than those with calcifications ($p < 0.0001$) and vesicular cysts ($p < 0.005$), and that patients with granulomas were also younger than those with coloidal cysts, although the difference did not reach statistical significance ($p = 0.367$).

Discussion

This study showed that patients with a single cysticercus granuloma in the brain parenchyma are younger than those with a single vesicular cyst, arguing against the classical hypothesis that granulomas are the end result of vesicular cysts destroyed by the host's immune system (Figure 2). Previous studies have attempted to evaluate the occurrence of age-related differences in the proportion of patients with parenchymal brain cysticercosis according to the evolutive stage of the parasites, with patients harboring “degenerating cysts” being younger than those with “viable cysts” [6–8]. Such studies, however, included patients with single as well as multiple cysts in the brain (most of which were in different evolutive stages), and evaluation of hosts' age according to the particular evolutive stage of cysticerci was complicated. To avoid that bias, we studied a highly selected population of patients harboring single parenchymal brain cysticerci, where it was more straightforward to evaluate any relationship between age and evolutive stage of cysticerci.

Previous studies, reporting age-related differences between the proportion of cysticercosis patients with “viable” and “degenerating” cysts, have not even considered the possibility of the currently proposed alternative hypothesis of early cysticerci resolution within the brain parenchyma. In contrast, they have attributed such differences to enhanced mechanisms of immune surveillance in young people, still assuming that the viable cyst stage occurred

much early in life. It is likely that cysticercus granulomas occur more often in young people as *Taenia solium* metacestodes are more prone to be acutely attacked and destroyed by the immune system soon as they enter into the human nervous system, by-passing or significantly shortening their time as viable or colloidal cysts.

Our study has some limitations. It is not possible to precise the moment of the infection in each patient and thus some or many patients with vesicular cysts may have been infected later than those with cysticercal granuloma. Neurocysticercosis-infected younger people may look for care later than older people, immune response at younger ages could differ, or more unlikely, our age differences may just have resulted by chance, given the relatively small sample size. In our view, the exposed age differences in the absence of any evident bias in patient selection, support that early disappearance may occur in a substantial proportion of cysticercal granulomas.

In patients with multiple parenchymal brain cysticerci, neuroimaging studies often show parasites in different evolutive stages, and has been common to assume that granulomas (seen in these cases) represent previously well-developed vesicular cysts that have been destroyed by the host's immune system. There has never been a satisfactory explanation to the fact that only a few parasites (in a given patient with massive parenchymal brain cysticercosis) are destroyed by the immune system while most others do not. And it has always been puzzling why some patients with heavy non-encephalitic cysticercosis only present with vesicular cysts while others also present with a few granulomas.

On the light of this alternative hypothesis of cysticerci involution, it is possible that the few granulomas that are seen in patients with an otherwise heavy non-encephalitic cysticercosis of the brain parenchyma [9,10] are the result of a re-infestation from repeated contact with a *Taenia* carrier. In these cases, an existing acquired immune system would more rapidly respond to the entrance of metacestodes to the nervous system and destroy them in the very early stages of infection. The same would not occur in patients with heavy non-encephalitic cysticercosis who are also *Taenia* carriers and infect and re-infect themselves by the fecal-oral route [9,11]. In such cases, the presence of the adult *Taenia solium* in the small intestine may favor the development of mechanisms of immune tolerance to nervous system invasion by cysticerci, and further implanted metacestodes would not be acutely destroyed by the host's immune system but would be allowed to transform into vesicular cysts.

As previously noted, our findings have potentially important therapeutic implications. It has not to be assumed that most vesicular (viable) cysticerci will be transformed into granulomas and destroyed by the host's immune system. Those parasites who will be destroyed are more likely to be attacked from the start, i.e., soon after metacestodes implantation in the brain parenchyma. Cysts appearing viable on neuroimaging studies must be treated with cysticidal drugs as it is unlikely that they will be spontaneously destroyed.

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Figure 1.

Box plot showing distribution in the age of patients according to the evolutive stages of parenchymal brain cysticerci.

Figure 2.

Diagram showing the traditional and the alternative hypothesis of cysticerci evolution within the brain parenchyma.