Current status and future perspectives on the medical treatment of neurocysticercosis

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Neurological disease resulting from neurocysticercosis (NCC) is common in most of the world. The variability in the biology of the infection and in its clinical manifestations has led to much confusion regarding appropriate management. Therapeutic options have evolved from surgery, symptomatic measures, and steroids, to include the use of anti-parasitic drugs and minimally invasive neurosurgery. This manuscript reviews the principles of medical therapy for NCC, from discussion of the need for individualized management approaches for each type of NCC to exploration of the most likely potential additions or modifications currently under study.

Keywords: Neurocysticercosis, Cysticercosis, *Taenia solium*, Peru

Introduction

Neurological disease resulting from infection with the larvae of *Taenia solium* or cysticerci (neurocysticercosis, NCC) is common in vast regions of the world.¹ The clinical manifestations of human NCC have been well known since the late 1800s and early 1900s.² Cysticerci in the central nervous system cause an extremely varied array of clinical manifestations due to the many possible presenting combinations of topography, stage, and number of lesions, as well as the presence and degree of the surrounding inflammation. The most common manifestations include seizures, headache, and intracranial hypertension. In most cases, symptoms develop years after the parasite initially establishes a viable cyst infection within the brain.^{3,4}

Decades ago, the management of NCC was restricted to surgery, symptomatic measures, and steroids. In more recent years (1978 onwards) anti-parasitic drugs, mainly praziquantel and albendazole, began to be used, although their adoption was not exempt of controversy.^{5–7} This manuscript will review the principles of medical therapy for NCC and the existing therapeutic options, and will explore the most likely therapeutic alternatives currently under study.

Types of NCC

Clinicians treating NCC must first take into consideration the type of disease present as this drives therapeutic approaches. Two major types of NCC exist depending on whether the cysts are located within the brain parenchyma or outside of it. This

distinction was evident early on to clinicians,^{8,9} who referred to extraparenchymal NCC as ‘malignant’ NCC due to its progressive nature and poor prognosis. In contrast, intraparenchymal NCC has a much better prognosis.¹⁰

Within intraparenchymal NCC, the numbers of lesions, their stage, and their location strongly influence prognosis and should be well defined (Fig. 1). A single lesion is associated with a better prognosis than when multiple lesions are present, particularly if it is already degenerating (‘single enhancing lesion’, ‘single degenerating cysticercus’, or ‘single cysticercal granuloma’; Fig. 2).^{11–14} Patients with massive infections, conversely, carry poorer prognosis. If a lesion resolves but leaves a calcified scar, the prognosis for seizure relapse is poorer.¹⁵ On the other hand, once all lesions have resolved and calcified, symptoms tend to lessen and are easier to control with appropriate medication.¹⁶

Extraparenchymal NCC is associated with more severe symptoms and worse prognosis than parenchymal NCC. It tends to cause intracranial hypertension and/or hydrocephalus, either by a large cyst producing mass effect or by blockage of cerebrospinal fluid (CSF) circulation. It is also associated with marked inflammation and increased proteins and cells in the CSF resulting from continued exposure to parasite membrane remnants.^{8,9,17} Several types of extraparenchymal NCC can be differentiated. Some of the most clearly defined include cysts or cyst masses in the Sylvian fissure,¹⁸ cysticercosis of the basal cisterns (basal subarachnoid NCC),^{8,9,17} or intraventricular NCC, which in turn shows particular

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Figure 1 Intraparenchymal neurocysticercosis. Viable cysts on magnetic resonance imaging (left), and calcified parasites on computed tomography (right).

characteristics depending on whether the cysts are in the lateral ventricles, the third or the fourth ventricle (Fig. 3). Subarachnoid cysts located in the convexity of the cerebral hemispheres tend to grow towards the inside of the parenchyma and behave as intraparenchymal lesions.

Symptomatic Treatment

A key initial concept in managing NCC is to ensure proper management of symptoms and to identify conditions that require urgent resolution, such as sustained seizure activity or intracranial hypertension. Emergency measures for these conditions follow the standard guidelines for management of status epilepticus or intracranial hypertension with or without hydrocephalus and do not require measures specific to their underlying NCC etiology, with the sole exception of surgical excision of cysts causing mass effect or blocking CSF pathways.

There are no particularities in the prescription of analgesics for headache in NCC. Similarly, antiepileptic drug management of seizure disorders associated with NCC follows usual guidelines. Monotherapy with a first-line drug should be instituted and safety and efficacy of anti-epileptic drug (AED) therapy should be monitored as in any other individual with seizures secondary to an organic focus. Due to low cost and broad availability, carbamazepine and phenytoin are the usual choices for clinicians in NCC-endemic regions.^{19,20} Most patients can be adequately controlled

at standard therapeutic doses. Whether AED can be safely withdrawn after the parasitic cysts have died is open to question. Some authors, particularly those in India where most of the cases of NCC present in younger individuals with a single degenerating granuloma, suggest restricting AEDs to 6 months only, in order to cover the period of time when there is significant inflammation around the dying cyst.^{21,22} Some of the published series provide early evidence in

Figure 2 Single brain enhancing lesion (post-contrast magnetic resonance imaging).

Figure 3 Extraparenchymal neurocysticercosis. Cyst masses in the Sylvian fissure (left), in the basal cisterns (basal subarachnoid neurocysticercosis, center), and intraventricular cyst in the fourth ventricle. Non-contrasted magnetic resonance imaging.

favor of this approach, but no controlled trial has yet proven this point. In cases with multiple cysts, the usual practice is to prescribe AED until there is a 2-year seizure free period. Thereafter, careful monitoring should be instituted if withdrawal is considered.

The use of steroids in NCC deserves further attention. Symptoms and signs are often directly related to local inflammation or intracranial hypertension, and both conditions respond, at least partially, to the administration of high dose steroids. Although steroids are beneficial in the short term, long-term steroid administration may cause serious side effects. Therefore, measures directed to solve the underlying problem caused by the NCC infection itself, such as removal of large cysts, cysts masses, ventricular cysts, or treatment of hydrocephalus, need to be implemented. A second indication for steroids occurs during anti-parasitic treatment of viable or degenerating cysts, when local inflammation is triggered by the attack of the drug on the cyst. Steroids are the primary tool to control the resulting perilesional inflammation and edema. Increased symptoms may also occur at the time of withdrawing steroids after the course of antiparasitic drug has finished.²³

Diverse regimes of steroids have been used, both in terms of drug choice (dexamethasone, prednisone, methylprednisolone, etc.) and duration. Steroids have been administered from a few days before the onset of antiparasitic drugs until a few days after the end of antiparasitic treatment, or have been administered only if moderate to severe side effects arise. Most centers would use dexamethasone at 0.1 or 0.15 mg/kg/day, divided into three doses concomitant with anti-parasitic treatment.^{23,24} Abrupt cessation of steroids should be avoided, and although a tapering period is advisable, there are no trials to suggest a particular regime.

Anti-parasitic Treatment

Anti-parasitic drugs kill living parasites, mostly by exposing them to the host's immune response which destroys the parasitic cyst through a slow process lasting weeks or months.²⁵ The effects and benefits differ greatly in intraparenchymal compared to extraparenchymal NCC and thus these two types of involvement are separately described below.

Anti-parasitic treatment in parenchymal brain cysticercosis

There has been much discussion in the literature regarding whether anti-parasitic drugs effectively kill cysts and whether anthelmintic treatment improves clinical outcome, defined as fewer seizures, in individuals with intraparenchymal NCC. Intuitively, the effects and clinical benefit of anti-parasitic regimes should be more evident in patients with multiple viable cysts, and less evident in patients with lesions that have begun their degenerative process and are already being attacked by the host's immune system. To date, evidence suggests that anti-parasitic drugs hasten the resolution of live parenchymal brain cysts, although it is unclear if a similar (evidently less marked) benefit is obtained in the treatment of degenerating cysts.^{13,26,27} In terms of symptoms, cyst destruction seems to be associated with: (1) an initial period of increased local inflammation associated with increased symptoms; and (2) fewer seizures in the long-term follow-up. In a double-blinded randomized trial, treatment accounted for a statistically significant decrease of 67% for seizures with generalization and a non-significant decrease of 41% for partial seizures.²⁴ In patients with a single degenerating cysticercus, most series find a clinical benefit of standard treatment with albendazole plus steroids despite non-conclusive evidence on faster radiological resolution of the lesion. However, it is not clear

whether this effect is due to the anti-parasitic agent, to the steroids, or to both.^{13,26,27}

Resolution of viable or degenerating brain cysts carries two additional aspects that have been not frequently been discussed. Patients feel much relieved to know that they no longer harbor a live brain parasite.²⁴ Although unproven, it is reasonable to believe that we also destroy other undiagnosed small cysts in areas where they could eventually grow and create serious clinical problems, particularly in the subarachnoid or intraventricular spaces.

Anti-parasitic treatment in extraparenchymal NCC

From all the published experience, it is evident that subarachnoid NCC, and likely a significant proportion of cases with intraventricular NCC, follow a progressive clinical course with parasitic growth, infiltration into neighboring spaces, and development of intracranial hypertension with or without hydrocephalus. Once intracranial hypertension has been taken care of, these patients require disease-specific interventions to control and kill the surviving parasite structures. A few may benefit from surgical removal, be it excision of ventricular cysts by neuroendoscopy^{28,29} or open surgery for the excision of large cysts or cyst masses in a single place. In most cases, however, parasite membranes or cysts are in regions of the brain that are not amenable to surgical removal, or where extensive involvement precludes surgery.¹⁷ In these cases, prolonged use of anti-parasitic treatment is the only feasible intervention and should be continued until convincing imaging or immunological evidence (negative for parasite antigen) suggests that no remaining live parasites exist.^{30–32} Clinically silent involvement of the spine is also common in basilar subarachnoid disease as reported in a recent publication that demonstrated spine invasion (mostly in the subarachnoid space) in over 60% of cases with basal subarachnoid NCC.³³ There is reason to believe that if left untreated, viable spinal cysts could eventually lead to chronic meningitis or to obstructive, mass effect-causing syndromes.

New or More Recent Treatment Options

Measures directed to improve the efficacy of anti-parasitic regimes are required. Combinations of anti-parasitic drugs, namely albendazole with praziquantel, have been anecdotally used, appear safe, and are likely associated with improved parasitocidal efficacy.^{34–36} A second option reported in the literature is to increase the dose of albendazole up to 30 mg/kg/day, although the small numbers of treated patients do not yet allow conclusions regarding the safety of these regimes.^{37,38} After appropriate pre-clinical work, human use of the veterinary drug oxfendazole may provide a more efficacious parasitocidal drug.³⁹ Other agents reported

to act against cysticercosis include the broad spectrum anti-parasitic agent ivermectin,⁴⁰ and the estrogen receptor modulator raloxifene,⁴¹ although further confirmation of these early reports is still missing.

Patients with only old, calcified lesions, can present with new or relapsing symptoms. Many times, symptoms are associated with contrast enhancement or edema around at least one of their calcified lesions.^{42–45} This phenomenon of peri-calcification enhancement and edema is not yet well understood but most likely corresponds to a reactivated immune response against parasite remnants persistent within the calcified lesion. Presently there is no evidence that the intuitively obvious use of steroids results in improved control of seizures in these cases.

As far as surgical intervention is concerned, the application of neuronavigation techniques to remove basal subarachnoid cysts has been only rarely reported.^{46,47} Also, excision of large Sylvian cysts even in the presence of other smaller cysts in a different location could greatly decrease the period of weeks or months of perilesional brain inflammation that follows anti-parasitic destruction of large parenchymal cysts.

The advent of modern neuroimaging and effective anti-parasitic agents has greatly improved the management of NCC over the past 20 years. With appropriate management, mortality and chronic morbidity are minimized. However, in most endemic situations, many patients are undiagnosed, improperly treated, or not carefully followed after treatment. A better understanding of the basis for symptomatic and anti-parasitic treatment, and translation of the advances to poorer, less equipped regions remain two of the most important tasks in NCC treatment for the near future.

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