Neurocysticercosis and epilepsy

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Abstract. Neurocysticercosis (NCC) is the most common parasitic disease of the central nervous system that affects thousands of people all over the world, mainly in Latin America (Mexico, Central America, equatorial zone, and Brazil), Asia (India and China), and Africa. Also because of the high immigration rates from endemic to non-endemic areas, NCC is now commonly seen in countries that were previously free of the disease. Although NCC can cause almost any neurological symptom, and the most common clinical manifestations are epilepsy and acute symptomatic seizures. NCC is the leading cause of epilepsy in the developing world. Epileptogenesis in NCC can be attributed to multiple causes, mostly of a direct or indirect effects of inflammation, gliosis, gene, and predilection for the cyst to travel to the frontal and temporal lobe. Recent community intervention studies show that educational and public health measures can reduce the incidence and prevalence of active epilepsy as well as preventable epilepsy from NCC in endemic populations.

Keywords: neurocysticercosis, epilepsy, prevention, imaging, epidemiology

Résumé. La neurocysticercose représente une des infections parasitaires la plus fréquente du système nerveux central ; elle touche des milliers de personnes dans le monde, en particulier en Amérique latine (Mexique, Amérique centrale, Zone équatoriale et Brésil), en Asie (Inde et Chine) et en Afrique. En raison des fortes migrations de zones endémiques vers des zones initialement protégées, la neurocysticercose est actuellement retrouvée dans ces nouvelles régions. La symptomatologie clinique est dominée par la survenue de crises symptomatiques et l’installation d’une épilepsie. La neurocysticercose est la cause majeure des épilepsies dans les pays en voie de développement ; les mécanismes associant des facteurs inflammatoires, gliotiques, voire génétiques ; la localisation frontotemporale du kyste est fréquente. Des mesures préventives d’éducation et de santé publique des populations en zones endémiques concourent à réduire l’incidence de la maladie.

Mots clés : neurocysticercose, épidémiologie, épilepsie, imagerie, prévention

Cysticercosis is a parasitic infection that results from ingestion of eggs from the adult tapeworm, Taenia solium (Garcia et al., 2003). Humans harbor the tapeworm that is acquired by eating poorly cooked pork containing cysticerci of Taenia solium. Ova or proglottids-containing ova are excreted in the feces and when ingested by pigs develop into cysts pri-
Neurocysticercosis (NCC) has become a serious public health problem in several countries in Latin America, Africa, and Asia, as in industrialized countries (Medina et al., 2002; Medina et al., 2005, Wallin and Kurtzke, 2004; Duron et al., 2006). Moreover, because of the recent increase in tourism, large movements of refugees and mass migration of individuals from endemic areas, NCC has become an increasingly worldwide-emerging infection (Wallin and Kurtzke, 2004; Duron et al., 2006). Moreover, because of the recent increase in tourism, large movements of refugees and mass migration of individuals from endemic areas, NCC has become an increasingly worldwide-emerging infection (Wallin and Kurtzke, 2004; Duron et al., 2006; Nicoletti et al., 2002; Medina et al., 2005; Rajshekhar et al., 2006; Medina and De Giorgio, 2002; Del Brutto et al., 2001).

**Epidemiology**

It is difficult to determine the prevalence and incidence of NCC due to the nonspecificity of its clinical manifestation and the lack of laboratorial tests that can be used to confirm the diagnosis in a large scale. The majority of people having NCC are asymptomatic.

This can be illustrated by a study in Salama, Honduras, a hyperendemic region for cysticercosis, where we found an overall cysticercosis seroprevalence of 17% (enzyme-linked immunoelectrotransfer blot seropositive), and 2.5% of supplied fecal samples contained *T. solium* eggs. In a second phase, 148 individuals from this population underwent computerized tomography (CT) scanning and neurological examinations. The CT results revealed cysts or calcified lesions compatible with NCC in 21%; the majority (84%) were asymptomatic (Sanchez et al., 1999a).

In developing countries, the nature of endemic taeniosis-cysticercosis is directly related to the religious trend and eating habits of the inhabitants. Human beings, therefore, acquire cysticercosis through fecal–oral contamination with *T. solium* eggs. The World Health Organization (WHO) considers NCC as the most important human neurological disease of parasitic origin and one of the principal causes of epilepsy in endemic countries (De Giorgio et al., 2004).

Almost 50,000 deaths attributable to NCC occur every year. Many more patients survive but are left with irreversible brain damage—with all the social and economic consequences that this implies. Several articles from different countries in Latin America consistently showed an association between around 30% of all seizures and cysticercosis (Duron et al., 2006; Román et al., 2000).

The published data confirm the worldwide distribution of NCC, especially in developing countries, for example, epilepsy is a major health problem in the rural areas of the Cordillera Province of Bolivia, with a prevalence of 12.3/1,000. In 2002, Nicoletti et al. performed a door-to-door survey study of prevalence of epilepsy in a rural village of Bolivia. They found 113 patients with epilepsy that were assessed serologically for antibodies against *T. solium*. The results showed an association between serological positivity for *T. solium* and epilepsy (OR 1.85) for all cases. A stronger association was found in those with partial epilepsy with a late onset of disease (OR 3.66) (Nicoletti et al., 2002).

In 1997, a door-to-door survey was done in rural Salama, Honduras. Among 6,473 residents surveyed, 151 people with epilepsy (prevalence rate: 23.3/1,000) were identified, 100 of whom had active epilepsy (15.4/1,000) on the prevalence day. Incidence was determined to be 92.7/100,000. Partial seizures with or without secondary generalization were common (92.2%). Symptomatic epilepsy was primarily due to NCC (37%) (Medina et al., 2005).

In Vellore, India a door-to-door survey of 50,617 inhabitants between the ages of 2 and 60 years was performed. Patients with active epilepsy were investigated with a contrast-enhanced CT scan and enzyme-linked immunotransfer blot (EITB) for cysticercal antibodies. The prevalence of active epilepsy was 3.83 per 1,000 people, and a diagnosis of NCC was made in 46 (28.4%) of the 162 patients (Rajshekhar et al., 2006) (table 1).

<table>
<thead>
<tr>
<th>Country</th>
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<th>Year</th>
<th>Population</th>
<th>Prevalence of Epilepsy</th>
<th>% NCC</th>
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<td>Ecuador</td>
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<td>Honduras</td>
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<td>2005</td>
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<td>India</td>
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<td>2006</td>
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<td>3.83</td>
<td>28.4</td>
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Table 1. Prevalence studies: Epilepsy due to neurocysticercosis
Natural History

NCC is acquired through the consumption of food contaminated with feces of a T. solium tapeworm carrier through fecal-oral contract (see figure 1). When the eggs of the tapeworm are ingested and exposed to the gastric acid in the human stomach, they lose their protective capsule and turn into oncospheres. There they cross the gastrointestinal tract and migrate through the vascular system to anywhere in the body including the brain. Once in the brain, the cyst has four stages: vesicular, colloidal, granular, and calcified granuloma. In the first stage, the larval cyst is viable. The scolex usually is identified, and there is minimal enhancement secondary to a host immune response. As the cyst deteriorates, it leaks fluid to the parenchyma, resulting in a strong immune reaction. In a further deterioration, it forms a nodule and finally calcified granulomas (Del Brutto and Sotelo, 1994; De Giorgio et al., 2004).

Epileptogenesis in Neurocysticercosis

The reason why some patients develop seizures and others clinical manifestation and others remain asymptomatic is due to individual differences between the number, stage, location of parasites and host immune response against the parasite (Del Brutto and Sotelo, 1994). Epilepsy and acute symptomatic seizures are the most frequent clinical manifestations of NCC,
as seen in 50-80% of cases, particularly in patients with compromised brain parenchyma (Medina et al., 1990; Rajshekhar et al., 2006; Del Brutto et al., 1994).

In a consecutive case study among 100 patients with late onset epilepsy in Mexico (Medina et al., 1990), some characteristic features of epilepsy due to NCC were found such as: high frequency of partial seizures, clinical manifestation depends on the localization of the parasite, and the high frequency of calcified granulomas as sequel of NCC without other signs of active diseases (Medina et al., 1990; De Giorgio et al., 2004; Rajshekhar et al., 2006; García and Del Brutto, 2005).

Epileptogenesis in NCC can be attributed to multiple causes, mostly of a direct or indirect effects of inflammation, gliosis, gene, and predilection for the cyst to travel to the frontal and temporal lobe (De Giorgio et al., 2004; Rajshekhar et al., 2006; Nash et al., 2004). New onset seizures are commonly associated with active cysts; seizures occur early in the disease in the setting of intense inflammation associated with viable or degenerating cysts rather than calcified granulomas. Cysts that are active and undergoing degeneration are the most epileptogenic, they can also occur later as a result of infarcts related to vasculitis and thrombosis of penetrating vessels from subarachnoid cysticercosis (De Giorgio et al., 2004; Del Brutto, 1999).

Chronic epilepsy is usually associated with calcified granuloma, it can be explained by the histology feature that accompanies this form of NCC sequel; around the granuloma an intense perilesional gliosis is found, forming a capsule of dense connective tissue with macrophages and foreign body cells. Gliosis is related to epileptogenic activity due to changes in the neuroglial relationship as the astroglia is unable to maintain a proper balance of electrolyte and neurotransmitters; these changes favor the development of epileptogenic neurons (Medina et al., 1990; De Giorgio et al., 2004; Nash et al., 2004).

In addition, calcification of the cyst is considered the last stage of the disease and was long considered innocuous; recent reports show a relationship between calcified perilesional edema and epilepsy (figure 2). It is well known that granulomas are the result of the host’s inflammatory response to viable or degenerating cystic larva, but the true pathophysiology of perilesional edema in calcification remain unknown (see Nash and Patronas, 1999; Del Brutto, 1999; Duron et al., 2003). One interesting aspect of the phenomenon is that only certain calcified foci are capable of developing perilesional edema, so only lesions that undergo perilesional edema would be predicted to contain or expose antigen while others would not (Nash and Patronas, 1999; Nash et al., 2004) (figure 2).

This idea is supported by reports from India, where it has been found that patients with epilepsy due to calcified cysticercosis show in its interior a recognizable scolex that develop perilesional edema and epilepsy. Demonstration of the scolex in a calcified lesion suggests that parasites did not undergo complete degradation and preserved its antigenic components intact, because of this, they are able to release the antigen into the surrounding parenchyma, resulting in inflammation and edema (Nash and Patronas, 1999; Nash et al., 2004). In the other hand, a variety of focal neurological signs have been described in patients with NCC, particularly those located in eloquent brain areas. The most common signs include: motor deficit, signs of pyramidal liberation, cerebellar ataxia, signs of brain stem dysfunction, and involuntary movements. These manifestations usually follow a progressive course and it is difficult to differentiate from neoplasms or other infectious processes of the central nervous system. In some cases, focal signs may appear suddenly, especially when related to infarct secondary to angiitis cysticerci (Rajshekhar et al., 2006).

Neuroimaging

Imaging studies have always been highly useful in the diagnosis of this disease. With the advent of brain imaging studies,
tomography and magnetic resonance imaging, the diagnosis of NCC was greatly improved. These imaging techniques depict the location and number of lesions, their stages and the degree of inflammatory response to the parasite (perilesional edema and blood–brain barrier breakdown) (Nash et al., 2004) (figure 3).

Revised diagnostic criteria for NCC consider that cystic lesions showing the scolex on CT or MR imaging are an absolute criterion for diagnosis of the disease. Suggestive lesions by neuroimaging (annular or calcifications) are among the major criteria. In fact, CT and MRI findings in parenchymal NCC depend critically on the degree of viability of cysticerci (Del Brutto et al., 2001; Rajshekhar et al., 2006; Nash et al., 2004; Herrera, 1996).

NCC cysts are located in the subarachnoid space, usually the basal cisterns and deep within the sulci. Other common locations include the hemispheric parenchyma at the gray matter–white matter interface and in the ventricles (fourth ventricle is most common) (Del Brutto and Sotelo, 1994; Osborn and Preece, 2006). Of these, the most characteristic findings are well-defined cystic lesions with the scolex inside. The scolex is visualized as a bright nodule within the cyst. This produces the so-called “hole-with-dot” imaging that is seen in some vesicular cysts located in the brain parenchyma, the subarachnoid space, or the ventricular system (Del Brutto et al., 2001; Herrera, 1996). Calcification, the final state of stage neurocysticercosis, is characterized on CT scans as calcified, nonenhancing nodule. On the other hand contrast annular lesions (single or multiple) are not specific and represent a diagnostic problem (Medina and De Giorgio, 2002; Gupta et al., 2002; Herrera, 1996; Lucato et al., 2007). Several entities, including brain abscesses, tuberculomas, and primary and secondary tumors of the nervous system, may present with similar lesions on CT or MRI. In these cases, even the practice of other complementary tests such as angiography or CSF study allows accurate diagnosis (Rajshekhar et al., 2006). It has been considered that CT is the first choice for detection of calcification over the MRI.

In ventricular neurocysticercosis, cystic lesions are viewed as distorting the ventricular system and cause asymmetric hydrocephalus. These cysts are usually isodense with CSF and are not well seen on CT, so it is often necessary to administer intrathecal contrast medium to confirm the diagnosis (Rajshekhar et al., 2006).

MRI allows better visualization of these lesions because the scolex can usually be identified and the signal of the vesicular fluid often differs from the CSF on T2-weighted slices (Rajshekhar et al., 2006). Although MR is not as sensitive to the presence of calcium as is CT, it has a greater sensitivity for

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**Figure 3.** Different stages of neurocysticercosis: 1) vesicular NCC, 2) cysticercotic encephalitis, 3) racemosus NCC, and 4) NCC calcifications.
contrast enhancement. This is particularly true in and around calcified lesion, that contrast enhancement usually occurs in patients in whom precontrast MR findings have shown active inflammatory reaction in the degenerating stage of the worm (Gupta et al., 2002; Herrera, 1996; Lucato et al., 2007; Del Brutto et al., 2001; Sheth et al., 1998). Overall, the MRI is better than CT for the diagnosis of NCC, especially for patients with cystic lesions in the skull base, brain stem, and spinal cord ventricular cavities.

Lesion localization and imaging techniques are also important to evaluate the evolution of the disease as well to differential diagnosis. Abscesses have a T2-hypointense ring whereas neurocysticercosis cysts are typically isointense except when they are in the ventricles where the ring is hyperintense on FLAIR images (Osborn and Preece, 2006). Ring-enhancing lesions due to toxoplasmosis are preferably located in the basal ganglia and lesions due to tuberculosis tend to be found in the cortical/subcortical, basal region of the brain and the posterior fossa. Metastases are generally multiple and may have very intense surrounding edema, a strong enhancement, and are more commonly localized at the grey-white junction. When a ring- or disc-enhancing lesion is found in the posterior fossa or brain stem, NCC is improbable (Osborn, 1994).

Diagnosis

Accurate diagnosis of NCC is based on assessment of the clinical and epidemiological data and the results of neuroimaging studies and immunological tests (Duron et al., 2006). Del Brutto et al. and Sanchez et al. provided important diagnostic criteria for NCC based on clinical, imaging, immunological, and epidemiological data (Del Brutto et al., 2001, Sanchez et al., 1999b).

These include four categories of criteria:
- absolute:
- histological demonstration of the cysticercus from biopsy of a brain or spinal cord lesion;
- evidence of cystic lesions revealing the scolex on CT or magnetic resonance images;
- direct visualization of subretinal parasites by funduscopic examination;
- demonstration of specific antibodies and/or antigens in cerebrospinal fluid;
- major:
- highly suggestive lesions of NCC on neuroimaging studies;
- resolution of intracranial cystic lesions after therapy with anticysticercal drugs;
- spontaneous resolution of small single enhancing lesions;
- minor:
- compatible lesions with those of NCC on neuroimaging studies;
- clinical manifestations suggestive of NCC;
- positive cerebrospinal fluid enzyme-linked immunosorbent assay for detection of anticysticercal antibodies or cysticercal antigens, and cysticercosis outside the CNS;
- epidemiological criteria:
- personal or household evidence of past or present T. solium infection;
- individuals coming from or living in an area where cysticercosis is endemic, and/or history of frequent travel to endemic areas;

Interpretation of these criteria permits degrees of diagnostic certainty (Del Brutto et al., 2001).

Prevention

NCC is one of a few conditions included in a list of potentially eradicable infectious diseases of public health importance (Medina et al., submitted to Epilepsia, 2010). The control strategy that seems promising at the moment is a combination of different available tools in order to interrupt or reduce the cycle of direct person-to-person transmission: mass human chemotherapy to eliminate the tapeworm stage, enforced meat inspection and control, improvement of pig husbandry and inspection, treatment of infected animals, surveillance, and identification and treatment of individuals who are direct sources of contagion (human carriers of adult tapeworm) and their close contacts, combined with hygiene education and better sanitation (Duron et al., 2006. Medina et al., submitted to Epilepsia).

Public health control and eradication of taeniasis and neurocysticercosis needs a full understanding of the life cycle of the tapeworm, and the intervention must aim different targets in order to interrupt this cycle. We performed a population follow-up study of epilepsy in Salama, Olancho between 1997 and 2005, where we defined prevalence of epilepsy due to neurocysticercosis (36.9% in 1997); a second study after 8 years evaluates the impact of public health and educational intervention program to reduce the incidence of symptomatic epilepsy. The intervention includes an educational program oriented to the general population, farmers, and butchers. The hygiene program provided the construction of potable water and latrine projects. The medical program include a mass treatment of human carriers of the tapeworm in school and preschool every 6 months and laboratory test (Kato-Katz) to scholars and general population. Results describe a significative reduction of the cases of epilepsy due to NCC in 2005 (13.9%) (Medina et al., submitted to Epilepsia).

Treatment and Prognosis

The therapeutic selection for NCC includes two cysticidal drugs (albendazole and praziquantel), steroids and nonsteroid anti-inflammatory therapy, antiepileptic drug treatment, and surgery for some cases (Garcia et al., 2002).
The praziquantel is an isoquinoline that has been used for the treatment of human NCC since 1979. Later studies showed that the use of praziquantel (50 mg/kg/day) for 8 to 30 days was effective in 60–70% of the treated cases (Del Brutto et al., 2001; García et al., 2002). Albendazole is a potent imidazole. This drug was used initially in 15 mg/kg/day dose for 30 days but later studies showed that treatment duration can be reduced to 8 days with equal results. Albendazole has better penetration into cerebrospinal fluid and kills 75–90% of parenchymal cysticerci (García et al., 2002).

García et al. (García et al., 2004) conducted a double-blind, placebo-controlled trial in which 120 patients who had living cysticerci in the brain and seizures treated with antiepileptic drugs were randomly assigned to receive either 800 mg of albendazole per day and 6 mg of dexamethasone per day for 10 days (60 patients) or two placebos (60 patients). In the albendazole group, there was a 46 percent reduction in the number of seizures during months 2 to 30 after treatment. This reduction, which was not statistically significant, was composed of a nonsignificant reduction of 41 percent in the number of partial seizures and a significant 67 percent reduction in the number of seizures with generalization. More of the intracranial cystic lesions resolved in the albendazole group than in the placebo group. This data indicates that the treatment with albendazole significantly improves the prognosis for recurrence of generalized tonic–clonic seizures in highly selected patients.

In Salama, Honduras, 33 patients with symptomatic epilepsy due to NCC were followed for 8 years. Diagnosis was made by a combination of clinical, epidemiologic, brain tomography, video-EEG, and laboratory criteria. The clinical evolution, persistence or remittance of seizures, was evaluated. We made a follow-up of 30/33 patients; 16 patients (53.3%) were seizure-free for more than 5 years, 13 patients (43.3%) persisted with seizures, and one patient died because of status epilepticus (Dubon et al., 2005).

Conclusions

Epilepsy is a very prevalent neurological disorder representing a worldwide burden of disease and stigma that affects nearly 1% of the population. Recent analyses concluded that the developing countries have high epilepsy prevalence rates that appear to be secondary to a high frequency of symptomatic “preventable” epilepsies (i.e., Neurocysticercosis).

Neurocysticercosis is responsible for increased rates of seizures and epilepsy in endemic regions. The most common form of the disease is the chronic calcified NCC, and there is increasing evidence indicating that it is not clinically inactive but a cause of epilepsy and seizures. Health and educational community interventions can reduce the incidence and prevalence of preventable epilepsy from NCC in endemic population of the world. □

References


