NEUROLOGICAL ASPECTS OF TROPICAL DISEASE

Neurocysticercosis and epilepsy in developing countries

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Abstract

Neurocysticercosis is a disease of poverty and underdevelopment. Little is known about the natural history of the infection in humans, but some of the mechanisms whereby the parasite remains silent and evades the host immune response are understood. Symptomatic neurocysticercosis usually results from host inflammatory response after parasite death, and the clinical manifestations can be diverse. There is no evidence that cysticidal treatment does more good than harm in addition to conventional antiepileptic treatment. Population control measures involving immunisation or mass treatment have not shown long term effectiveness.

Epilepsy, similarly to neurocysticercosis, is a largely unrecognised but increasing burden on the welfare and economies of developing countries. The technology of drug treatment and psychosocial rehabilitation is well known but requires widespread and effective dissemination at low cost. There is little epidemiological data on risk factors for epilepsy in developing countries on which to base prevention strategies. The public health prioritisation of chronic disorders such as epilepsy remains a challenge for policy and practice in developing countries.

For both neurocysticercosis and epilepsy, there is a dilemma about whether limited public resources would better be spent on general economic development, which would be expected to have a broad impact on the health and welfare of communities, or on specific programmes to help individual affected people with neurocysticercosis and epilepsy. Either approach requires detailed economic evaluation.

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The immense burden of epilepsy is a growing problem in developing countries where the incidence of epilepsy may be higher than in western countries.[1] Three quarters of the 50 million people with epilepsy live in the poor countries of the world and up to 94% are untreated.[2 3] Extending appropriate services to these people will be one of the great challenges of the new millenium. Unfortunately little is known about the causes of epilepsy in developing countries. However, many studies from Latin America have shown that infection of the brain by the larvae of the pork tapeworm *Taenia solium* is an important cause of epileptic seizures in endemic communities.[4–6] Many recent reviews have covered in detail the pathology,[7] parasitology,[8] clinical features,[6] and diagnostic criteria[9] of neurocysticercosis. This review concentrates on recent developments in the immunopathogenesis of neurocysticercosis, the controversy over clinical classification, and the evidence base for different treatment approaches. The challenges for the population control of cysticercosis and epilepsy in the developing world are summarised.

Neurocysticercosis

EPIDEMIOLOGY

Taenia solium is endemic in Latin America, India, and China, and may also be endemic in sub-Saharan Africa, although there are few studies.[10 11] Poor hygiene and living conditions, allowing pigs access to human faeces, put people at risk of developing cysticercosis.[4 12–15] In endemic countries, the disease is also widely prevalent in urban, middle class areas.[16] Migration from the countryside and the rise of urban slums obviously influence the changing epidemiology of cysticercosis. *T solium* infections have also been imported by migrant workers into the United States.[17]

Neurocysticercosis is of great economic relevance, resulting from the cost of medical treatment, lost working days, and losses due to livestock condemnation. A minimum estimate of the cost of admissions to hospital and wage loss for neurocysticercosis in the United States (a non-endemic country) was $8.8 million annually, wheres estimated treatment costs in Mexico were $89 million, and Brazil $85 million.[18]

PATHOLOGY

Life cycle biology

In the first stage, the human host ingests diseased (measly) pork containing viable cysticerci, from within which the scolex of the metacestode evaginates in the gut and attaches to the intestinal mucosa.[8] The tapeworm

matures over 2–3 months to achieve a length of 2–7 m. Gravid segments may contain 50–60 000 eggs which are passively released in small groups in faeces, two or three times a week, often unknown to the host. After ingestion, eggs hatch and activate in the pig small intestine and develop in striated muscle and the CNS. When humans accidentally become intermediate hosts by ingesting eggs, the life cycle is completed in a similar way in muscle, skin, and CNS.

Human pathology

Our understanding of natural human infection depends on studies of expatriates from endemic zones, and postmortem data. Initially, there is an asymptomatic period after egg ingestion lasting many years or even for life. The time between infection and symptoms in neurocysticercosis depends on number, size, type, condition, and site of cysts in the brain. A study of British soldiers with neurocysticercosis returning from India showed that most developed seizures 2–8 years after infection.[19] Postmortem studies in endemic zones show that about 80% of infections are asymptomatic.[20] However, the risk of intracranial infection after *T solium* egg ingestion is unknown.

IMMUNOLOGY AND PATHOGENESIS

Evidence from animal models and clinical studies shows that cysticerci remain clinically silent as a result of active immune tolerance, and that symptomatic parenchymal disease occurs at the time of larval degeneration or death by cysticidal therapy. Human neurocysticercosis treatment studies show rises in IgG, interleukin-2, and neopterin in the CSF.[21] A study of patients with hepatic echinococcosis (another human cestodiasis) suggests that a switch in IgG subclass response from IgG1 to IgG4 might occur as the disease progresses from its asymptomatic to symptomatic stages.[22] Recently it has been reported that eotaxin and interleukin-5 concentrations are raised in the serum of patients with symptomatic neurocysticercosis, and interleukin-5 and interleukin-6 concentrations are also raised in the CSF, possibly indicative of an acute phase response.[23]

Epidemiological and clinical findings suggest that individual immunological responses to cysticercosis might have a genetic basis. Firstly, Guatemalan population studies have shown no association between *T solium* seropositivity and epileptic seizures in a highly endemic area.[12] This could be explained by differences in population genetics or parasite strains, although there is little evidence of the second.[8]

Secondly, seizures are more common with multiple lesions,[24] and leucocyte chemotaxis is impaired in patients with multiple neurocysticercosis lesions.[25] Multiple lesions are much less common in India than in Latin American countries.[26] Preliminary association of epilepsy in neurocysticercosis with HLA type I has been reported in India.[27] HLA-DR polymorphisms have been demonstrated in various infections including leishmaniasis, onchocerciasis, filariasis, hepatitis, and malaria, whereas polymorphisms of tumour necrosis factor α and of the membrane protein ICAM-1 are associated with increased risk of death from cerebral malaria.[28–30] It is hypothesised that HLA differences might also determine the risk of intracranial infection or symptomatic parenchymal disease in neurocysticercosis.

CLINICAL PRESENTATION

There are wide variations of clinical manifestations of neurocysticercosis. These are a consequence of inflammation around a cyst(s), space occupation and impedance to the flow of CSF, less commonly meningeal or vascular inflammation, and non-CNS disease. Seizures are the most common symptom in 70%-90% of patients.[6 9 26] These may occur both when a cyst is degenerating,[31] or around a chronic, calcified lesion.[32]

Electroencephalography shows focal or generalised abnormalities, or no abnormality in neurocysticercosis epilepsy. Examination of CSF in neurocysticercosis usually yields mild abnormalities such as increased protein or pleocytosis, not always eosinophils. Interestingly, the proportion of seizures reported as generalised tonic-clonic ranges from 28% to 68%,[5 33 34] despite the presence of a focal lesion.

Some 10%-20% of patients present with ventricular cysts, sometimes also with seizures or with meningeal inflammation. Symptoms include nausea, vomiting, headache, ataxia, and confusion. Focal neurological deficits are uncommon. Patients with cysts in the basal cisterns can present with meningeal signs, hydrocephalus, vasculitis, and stroke.[9] Rarer neurological manifestations have also been reported—namely, altered mental state; spinal cysticercosis with radicular pain or paraesthesiae, or progressive cord compression; ophthalmic cysticercosis; migraine headaches; and neurocognitive deficits.[9] Cysticercal encephalitis, with multiple parenchymal cysts, an associated inflammatory response, and diffuse cerebral oedema is a rare presentation, often in young girls; these patients are at risk of severe neurological sequelae. Intracranial hypertension and meningeal neurocysticercosis are uncommon in India.[35] Subcutaneous cysticercosis is much more common in China than in Latin America or India.

Single enhancing CT lesions

Solitary enhancing CT lesions have commonly been described in India.[36 37] It is still unknown why single lesions are a more common presentation in India than multiple lesions. These single lesions are seen as areas of increased signal on MRI, and are mostly attributed to neurocysticercosis on the basis of resolution or calcification over months with conservative treatment (antiepileptic drugs). Tuberculosis is the primary differential diagnosis, but pyogenic abscess, fungal infection, vasculitis, and neoplasms can account for similar appearances.[7] Criteria for differentiating cysticerci and solitary tuberculosis lesions have been proposed by Rajshekar *et al*.[38] In their histologically established series, intracranial hypertension and progressive neurological deficit were not seen

with neurocysticercosis; all neurocysticercosis lesions were less than 20 mm in size, mostly regular in outline, and not associated with midline shift.

Diagnosis

Neuroimaging is essential to the diagnosis of neurocysticercosis (see fig 1 and fig 2) Brain MRI is superior for showing intraventricular or subarachnoid cysts, and for showing inflammation around a cyst,[39] whereas CT is better for showing the calcification of inactive lesions. There may be single or multiple cysts in different pathological stages. Carpio has proposed a classification system that corresponds to the viability of the parasite: active, transitional, and inactive.[7] In the active stage, the cyst is asymptomatic, and on CT appears as a rounded, hypodense area, or with CSF-like signal on MRI. Both MRI and CT can show the presence of an eccentric mural nodule (the invaginated scolex), an appearance, when multiple, which is pathognomic of neurocysticercosis (starry night effect). As the cyst degenerates, it goes through a transitional stage, with diffuse hypodense appearance and irregular border on CT, enhancing with contrast. On MRI T2 images, these show as low signal areas. Finally when the cyst dies, it may disappear or end up as an inactive calcified nodule of homogenous high density on CT, or low intensity on proton weighted MRI.

Standard enzyme linked immunosorbent assay (ELISA) techniques have disappointing

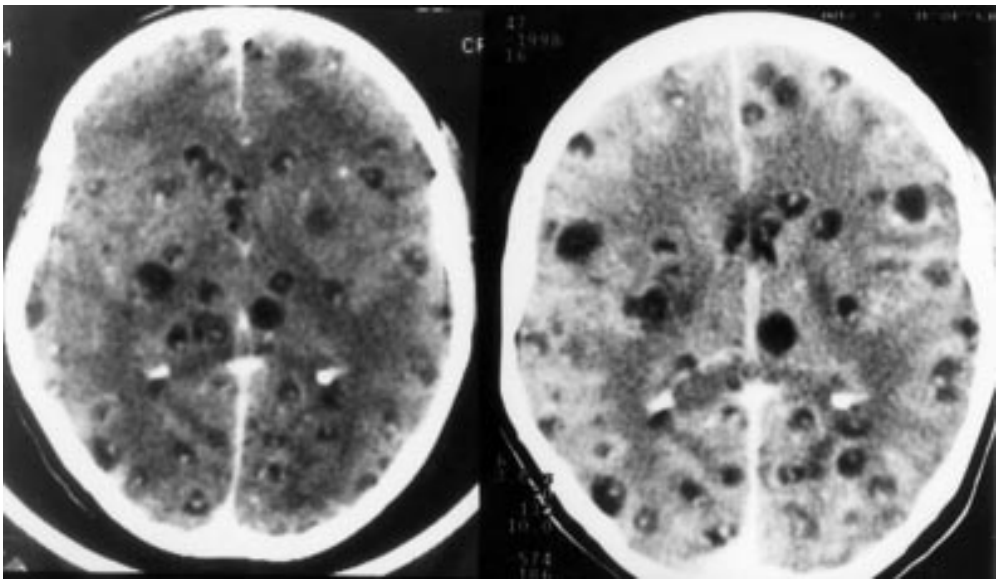

Figure 1 Postcontrast CT of a patient with seizures and intracranial hypertension syndrome, who received albendazole treatment. Left: multiple active cysts with the scolex in their interior (vesicular phase) and calcifications. Right: 16 months after treatment more cysts appeared, and some of them increased in size.

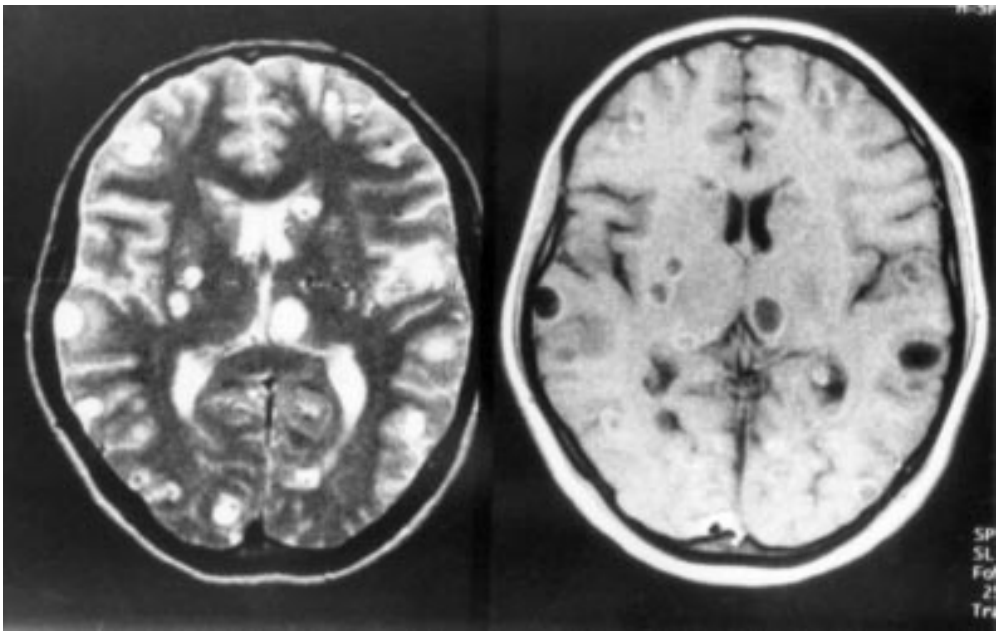

Figure 2 Brain MRI of the same patient of fig 1 (7 months after last CT), who received additional treatment using praziquantel. Left: T2 weighted MRI shows multiple cysts. Right: gadolinium enhanced T1 weighted MRI shows cortical active cysts on parietal lobes and multiple transitional cysts disseminated in both hemispheres.

sensitivity and specificity in routine clinical or epidemiological use.[40 41] False negative serology can result because of immune tolerance, inactive disease, or localised antibody production in the CSF. False positive serology can result from past infection with *T solium* or cross reactivity with other helminth species. Newer enzyme linked immunoelectrotransfer blot (EITB) assays on serum or CSF have much higher claimed sensitivity (95%) and specificity (100%)[42] in Latin American samples.

However, EITB test properties are less good for solitary enhancing CT lesions in India.[43] In Ecuador, more than 50% of patients with neurocysticercosis diagnosed by CT were negative by EITB test; conversely, 18% with positive EITB had neurocysticercosis parenchymal lesions on CT[16] indicating that EITB and neuroimaging should be used in conjunction to increase diagnostic sensitivity. Recently, an antigen detection assay specific for viable metacestodes in CSF has been created.[44] Immunodiagnostic kits are unfortunately difficult to obtain in endemic countries, so the use of the EITB and other special assays may only be restricted to research studies.

Del Brutto *et al* have proposed international diagnostic criteria for neurocysticercosis using a combination of clinical, radiological, serological, and epidemiological factors.[45] These have been criticised for complexity and difficulties in clinical and epidemiological application, and a satisfactory consensus is yet to be reached.[46]

MANAGEMENT: CASE AND COMMUNITY

Clinical case management

The presence of viable parenchymal cysts is not usually associated with symptoms. Most patients with neurocysticercosis present with seizures and in most cases (75%), these are easily controlled with antiepileptic monotherapy with eventual remission. The natural history of these lesions is for resolution within 2 years.[24 47] Clinical controversy has centred around the role of cysticidal agents and steroids for epilepsy associated with symptomatic neurocysticercosis. Cysticidal agents in current use for neurocysticercosis include praziquantel and albendazole. Praziquantel has the disadvantage that its hepatic metabolism is inducable by phenobarbital and phenytoin. Cysticidal therapy seems to hasten radiological resolution of cysts but can be associated with an exacerbation of neurological symptoms and there is also the possibility of massive cerebral oedema and death in some patients who have multiple cysts.[48] Some authors have advocated simultaneous administration of steroids to reduce the inflammatory response and exacerbation of symptoms, but the safety of this has not been evaluated. There have been claims that more patients remain seizure free after cysticidal treatment.[32] Randomised clinical trials of cysticidal therapy versus placebo for neurocysticercosis have not shown any clinical benefit of cysticidal therapy.[49 50] A possible increase in risk of hydrocephalus, and increased seizures during treatment, was also identified in the treated group.

Community treatment and prevention

Eradication of cysticercosis should be possible by removing it from either pig or human hosts, or both. Reform of animal husbandry techniques, meat inspection procedures, and adequate cooking of pork are difficult approaches and of limited relevance in developing countries, where pigs are free roaming, or raised by subsistence farmers who cannot afford enclosed pens or proper animal feed, and meat is sold off outside the abattoir system. Vaccination of pigs and immunotherapy have been proposed as measures to break the parasite life cycle. Partial protection against porcine cysticercosis has been demonstrated.[51–53] Taenicidal eradication in humans may have adverse effects in people with occult neurocysticercosis, who may become ill when cysticerci die.[54] Studies of mass treatment with praziquantel may produce early benefit, but longer term evaluation shows no lasting impact.

Management of epilepsy in the developing world

EPIDEMIOLOGY

Epilepsy affects 5–10/1000 population throughout the world, with 75% of cases arising in childhood.[1] Neurocysticercosis is a major cause in developing countries,[4 5 12] but the relative contribution to all incident cases is unknown. Malaria and other parasites are associated with epilepsy.[55–57] Studies in Ecuador, Tanzania, Nigeria, and Pakistan have consistently found higher prevalence of epilepsy in rural than in urban areas using identical methodologies, further suggesting that infectious diseases may be an important aetiological factor for epilepsy in the developing world.[58–61] New epidemiological associations have been suggested between low body mass index, previous adverse reproductive experience, recent infective illness, and risk of epilepsy in children.[62–64] These interesting associations merit further study in developing countries, as they may disclose new mechanisms of risk and risk interaction for focal brain damage in childhood.

IMPACT

Everyday conditions for most of the world's poor are radically different from the experience of the western hospital outpatient. This context must be appreciated when considering the impact of epilepsy. The primary concern of families is often subsistence, and this shapes their attitudes to health and their contact with health services. Poor female literacy, often associated with underdevelopment, is an important influence on child health, whereas cultural and religious beliefs may also impinge on health related attitudes and practices.

Few studies have measured the impact of epilepsy on family life in developing countries. One population study of childhood epilepsy in rural India has shown that epilepsy has pervasive effects on social adjustment, which probably do not spontaneously resolve.[65] One third of children had motor or cognitive impairment and one third had intractable seizures. Only 50% went to school compared with over 95%

of their peers. Difficulties of parental adjustment, reported in north American studies,[66] were even more prominent in rural India, with marked maternal depression.[65] A strong social support network helped with parental adjustment.[65]

The economic impact of epilepsy has not been prospectively studied, but estimates from rural India suggest that the social and financial cost of hospital attendance is a major disincentive to continued treatment.[65] India (until recently) and other countries also have laws that discriminate against people with epilepsy—for example, with regard to marriage, employment, and insurance.[67] For practical purposes epilepsy must therefore be considered a disability and interventions should consider all aspects.

INTERVENTION

The type of intervention required, as suggested by studies of impact, and the necessary resources for service delivery are not widely available in the developing world. The "treatment gap" refers to the proportion of people with epilepsy untreated with antiepileptic drugs on any given day. The estimates in developing countries range from 80%-94%.[3] The causes of the treatment gap have not yet been systematically studied but they must be multiple, overlapping, and varying between countries. They may be considered at infrastructural, health sector, and community levels. For example, some countries may have established health systems but lack finances or reliable drug supplies. In some communities, there may be preferred alternatives to antiepileptic drug treatment. Generalisation is difficult. There are several themes that should be considered in the design of services in developing countries: ascertainment, disability, intractability, sustainability, equity, community involvement, and financing.[68]

The first issue is that of ascertainment. In many communities, epilepsy is a stigmatising disorder. House to house surveys are thought to be an epidemiologically sensitive method of finding cases. However, in our experience, they may cause unnecessary distress to families and the community. They are an expensive method, and sensitivity can be as low as 60% because of concealment.[69] The use of key informants, or leading members of the community, to identify people with epilepsy, has several distinct advantages. These include the opportunity to explain the aims of the service, finding out local priorities, and working with the community to overcome social barriers to integration. Strong community involvement is also a key element to ensuring sustainability.

A third of people with epilepsy have physical or cognitive difficulties. Whether or not seizures can be controlled, people with epilepsy need to resume as normal a life as possible. This requires a holistic assessment and formulation of an action plan with the community. This is especially important for children's development. This kind of intervention can only be planned and executed at a local level. The disability aspect of epilepsy is perhaps the most important and neglected aspect of intervention.

An intractability rate of one third should be expected. Ideally, primary facilities need to have links with specialists for advice and referral. In some areas epilepsy surgery programmes may be offered, but opportunities for postoperative rehabilitation and reintegration should be major considerations before planning surgery.

The treatment and rehabilitation of people with epilepsy is a long term matter, and so it is essential that services, once started, continue in a predictable way. Sustainability of health programmes is associated with strong community ownership, political will, and stable financing. Services should be cheap to set up and run, and this can be achieved at marginal cost by integrating epilepsy services alongside existing medical or welfare programmes, rather than starting a new vertical programme.

It is well known that those most in need of health provision are often least able to gain access to it. A central tenet of primary health services is equity. Our studies of dropout showed that a significant proportion could not afford time away from home or work to attend clinics, despite wanting to continue follow up.[65a] Hospital based services (in India) have very high attrition rates and so are ill equipped to provide necessary long term monitoring and treatment.[65] Flexibility in delivering services is therefore important to prevent attrition, ideally to the door if necessary. Services can be extended through community mental health and community based rehabilitation agencies, in both state and non-governmental sectors.[70] A community based approach can fulfil the essential aim of rehabilitation through effective case holding, thus minimising dropout. Low cost is also a major motive for reattendance, and therefore precludes expensive investigations or new generation drugs at first contact. Community based services still need to be affordable by their users.

Expertise in dealing with epilepsy has to be devolved to local health personnel to attain wide coverage. In many countries, epilepsy is not covered in the medical undergraduate curriculum, and most general practitioners are not familiar with routine management. Training is required at all levels, and systems of monitoring and evaluation designed for local use.

The use of phenobarbital as first line agent remains very controversial among clinicians. Although the most widely available antiepileptic drug in the world, and effective against many seizure types, its use has been discouraged in some quarters because of concern about excessive side effects in children. However, a recent clinical trial has established that phenobarbital is indeed acceptable as a first line antiepileptic drug for children in India,[71] and this is supported by a population study which refutes the notion that it is often used as a drug of misuse or for suicides among adults.[72] In many parts of the world, the supply of antiepileptic drug is unreliable, and the choice may be between phenobarbital or nothing.[73]

Epilepsy control programmes will need detailed resource planning. Training, drugs, and infrastructural development will need costing. The non-governmental and private sectors play an increasing role in the provision of primary services in India. Physical standards are often superior, and acceptance by mothers and children is high. Many non-governmental organisations are oriented towards community development and use village health workers. A collaboration of sectors is necessary in countries like India where the public system alone cannot achieve wide coverage.

The unmet needs of people with epilepsy in developing countries are obviously more complex than providing treatment with drugs. Appropriate interventions must consider the medical, developmental, and psychosocial needs of people with epilepsy, as well as being financially, geographically, and culturally accessible. Legal barriers to social advancement also need to be removed. Research is urgently needed on the population risk factors for epilepsy in developing countries, and action has to be coordinated against known preventable causes.

Conclusions

Relatively little is known about the epidemiology of neurocysticercosis, and cysticidal treatments have been advocated without clear evidence for overall benefit in humans. Diagnosis may be difficult even with neuroimaging and serological facilities. Neurocysticercosis is a major cause of acquired epilepsy in Latin American countries. The economic burden of both are not well quantified. Community prevention and eradication of neurocysticercosis depends on general infrastructural development. Most people with epilepsy in developing countries do not have access to appropriate management. The major challenge for the future will be to develop primary level services that provide appropriate interventions for these communities.

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