Neurocysticercosis: Parasitology, Clinical Presentation, Diagnosis, and Recent Advances in Management

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'Ciggs whose meat is tender have bladders which are like hailstones in the region of the thigh, neck and loin. If they are few in number, the meat is leaner; if there are many, the meat becomes soft and filled with serous fluid.' Aristotle, History of Animals, 384–322 BC

Cysticercosis, which is the most common parasitic cause of neurological disease in man, consists of infection by the larval stage (Cysticercus cellulosae) [1] of the pig tapeworm Taenia solium. The disease was described in pigs by Aristophanes and Aristotle in the third century BC, but Paranoli is credited with the first human account (involving the corpus callosum) in 1550 [2]. The term cysticercus was first used by Laennec. One of the largest series of cases was documented by Dixon and Lipscomb in British soldiers and their families in India [3]; 92 per cent of 450 affected individuals described had a history of epilepsy. Although accurate information on prevalence rates is rarely available, the disease is known to be endemic in all continents with the exception of Australasia [4]; however, even there cases in immigrants are now being identified. Exceptionally high rates exist in Latin America – from Mexico to Chile. In Mexico City 1.4–3.6 per cent of autopsies in the general population provide evidence of cysticercosis [1]; the disease accounts for approximately 10 per cent of neurological admissions, as well as up to one-third of craniotomies for intracranial space-occupying lesions. Important foci exist in the USSR, China, India, Pakistan, the Philippines and Indonesia [5], and the disease occurs sporadically throughout Africa. Although now rare in northern Europe, it remains a problem in the Iberian peninsula and the Slavic countries. In north America, the disease is overall unusual; however, during the last decade it has become a significant problem in immigrant populations [6]. Cysticercosis is overall unusual in Jews and Muslims because pork consumption in these ethnic groups is generally low; however, this fact does not prevent ingestion of T. solium eggs in contaminated food or water. This, and not uncooked pork ingestion is the cause of human cysticercosis.

The highest prevalence rates therefore exist in communities where there is a close contact between man and pigs, pork is eaten raw or undercooked, and most importantly where hygienic standards and practices are low. Affected communities are often rural ones [5]. Faecal contamination of foodstuffs is the usual source of infection; however flies have been shown to play a
part in the spread of *T. solium* eggs, and cases caused by aberrant sexual practices and witch doctors have also been recorded. In Irian Jaya, an ‘epidemic’ of epilepsy which resulted in villagers suffering from extensive burns after falling into their domestic fires, had its origin in a gift of infected pigs from Bali. Recent examination of a random sample of 242 Ekari people in Irian Jaya revealed that 42 had palpable cysticercal nodules [5]; eight of them gave a history of fits and six of burns.

**PARASITOLOGY**

Man is the sole definitive host for adult *T. solium* and is therefore the only source of eggs [1]. Following ingestion of viable cysticerci in contaminated meat from the intermediate host (the pig) – ‘measly pork’ – the scolex (or head) when digested out of the cyst attaches to the small-intestinal wall. Here, it grows into a mature tapeworm in five to 12 weeks and may live in the human small intestine for up to 25 years; it is unusual (but not impossible) for more than one adult to be present simultaneously. The scolex anchors itself by means of four muscular suckers and a double row of hooklets which are present on the rostellum; the remainder of the worm (the strobila) which ultimately consists of up to 1000 proglottids or segments, and varies from 2 to 10 m in length, may extend into the ileum. Gravid segments break off from the worm’s distal end and may be swept out intact in faeces; alternatively, gravid segments disintegrate in the colon with the liberation of thick-walled eggs (31–43 μm in diameter) which after elimination in faeces may remain viable in soil for several weeks. The cycle is completed when eggs (via human faeces) are ingested by pigs with the eventual production of cysticerci in various organs, especially skeletal muscle. If human cannibalism both existed and was widely practised, this could theoretically play a significant role in the life-cycle. Treatment of *T. solium* infection is with praziquantel, niclosamide, dichlorophen or mepacrine [1, 4]; some physicians follow chemotherapy with a laxative some two to four hours later to expel any residual *T. solium* eggs.

Human cysticercosis arises when man becomes an incidental intermediate host [1]. Eggs are ingested in food or water contaminated by human faeces. They begin to hatch in the stomach (the egg wall is dissolved by gastric secretions) and the process is completed in the duodenum. Here, oncospheres emerge, penetrate the intestinal mucosa and enter local lymphatics and mesenteric vessels. From there they are transmitted to many organs: e.g. central nervous system, skeletal muscles, heart, eye, and oral cavity, in addition to subcutaneous tissues. Within two to three months, the oncospheres lose their hooks and develop into fluid-filled ‘bladder-worms’ or cysticerci. External auto-infection can also give rise to cysticercosis, i.e. an individual harbouring an adult *T. solium* may infect him/herself via the faecal–oral route. Although in theory internal auto-infection could result from a reversal of peristalsis, so that gravid proglottids would enter the stomach from the small intestine with the subsequent hatching of eggs, this has never been proved and is undoubtedly a rare event [4].

As they mature in various tissues, cysticerci evoke a chronic lymphocytic and granulomatous reaction [1]; the capsule subsequently fibroses and is surrounded by neutrophils, eosinophils and later lymphocytes, plasma cells and giant cells. In the brain, the cyst lies within a wall of neuroglia which later undergoes degenerative change, and appears as a discoloured ring which is walled off from normal brain tissue [4]. The morphology of the scolex of *C. cellullosae* in cerebral tissue has been described in detail [7]. Although some evidence of protective immunity has been demonstrated in cattle against the related species *C. bovis*, only very limited evidence of this is available in human disease. The activated embryo (oncosphere) contains an antigen which acts against larval cysts in the tissues. These space-occupying lesions may persist for up to 20 years. In muscles and some other soft tissues, the cyst wall may collapse, becoming flattened, and after calcification take on a spindle- or oat-shaped form. However, in the brain the cysts
Neurocysticercosis remain oval or spherical. Dying cysts are surrounded by acute inflammation associated with tissue damage. When dead, they either resolve or remain in situ and subsequently calcify (this may occur after three years, but takes much longer in the brain). As calcification occurs, symptoms usually subside and may disappear completely.

CLINICAL PRESENTATION

Presentation of disease is usually from two months to 30 years after infection (mean five years [8, 9]); most individuals at presentation are aged 20–50 years. The initial symptom is usually awareness of small subcutaneous nodules or intramuscular swellings; a myositis may also be present. I have seen a patient who had had 84 subcutaneous nodules removed surgically on the supposition that they were caused by an Onchocerca volvulus infection; histological examination showed them to be C. cellulosae. Every organ may be affected by this parasitosis; symptoms depend on the number, age and location of cysts. If neurological involvement does not occur, cysticercosis remains a benign disease. One estimate is that the brain is affected in 60 per cent and the eye in 3 per cent of infections [1, 8, 9]. Any part of the central nervous system can be affected; symptoms result in approximately 50 per cent of cases. Fits, increased intracranial pressure and stroke are the commonest manifestations [6, 8–11].

The possibility of neurocysticercosis should be considered in anyone suffering from fits who has resided in an endemic area [4]. Clinical presentations in a large series of cases have recently been recorded at Los Angeles [10]. Although the presentation may be a mixed one (multiple cysts are present in over 50 per cent of patients), clinical neurocysticercosis can be roughly divided into four main groups [1, 4, 12].

Parenchymal cysts. These are found in the majority of patients, and cause fits, acute or progressive focal abnormalities and raised intracranial pressure. Epilepsy is usually caused by fresh, live cysts, and may be either focal (Jacksonian) or general.

Meningeal cysts. These are often in the basal meninges and occur in approximately 50 per cent of affected patients. There may be intense inflammation with obstructive hydrocephalus, arterial thromboses and stroke.

Ventricular cysts. These may be free-floating, or attached, and are most common in the fourth ventricle. They are found in approximately 15 per cent of affected patients. They become symptomatic when they block the aqueduct of Sylvius causing raised intracranial pressure, which is associated with severe headaches and vomiting.

Spinal-cord cysts. These are found in 3 per cent of cases, and cause arachnoiditis with transverse myelitis, or signs of a local mass lesion.

Other clinical manifestations which have been described in another series of cases include cerebral infarction, ocular involvement, dementia, spinal arachnoiditis, thrombosis of superficial cortical vessels by chronic meningitis (which gave rise to ‘cerebrovascular events’), and a hemisensory deficit [9]. Korsakoff’s psychosis, Parkinson’s disease, motor neurone disease, a variety of pituitary fossa syndromes and isolated cranial nerve palsies have also been recorded [9]; cerebellar syndromes, diplopia, dementia, schizophrenia, manic-depressive disease, dysarthria and the Brown–Séquard syndrome are others [3]. In children an acute encephalitis may account for the initial clinical presentation [6, 14]. A particularly severe and aggressive
of disease is a racemose meningobasal form [11, 13]; groups of cysts arborize into extensive grape-like clusters around the basal cisterns with production of hydrocephalus and dementia. Ocular cysticerci float freely in the anterior and vitreous chambers, or adhere to subretinal tissue [1]. The latter may cause papilloedema [9], haemorrhage and vasculitis of the disc. In the vitreous chamber, larvae may cause clouding, choroidoretinitis and retinal detachment. The lacrimal glands and eyelids may also be affected.

Idiopathic epilepsy, multiple intracranial space-occupying lesions, chronic meningitis and other causes of raised intracranial pressure can be mimicked. Differential diagnoses also include tuberculosis (especially tuberculomas), coccidioidomycosis, cryptococcosis, neurosyphilis, sarcoidosis, and primary and secondary malignancies affecting the central nervous system [1, 9]. In certain tropical locations, the following should also be considered: hydatidosis, angiostrongyliasis ('eosinophilic meningitis'), gnathostomiasis, paragonimiasis, schistosomiasis, filariasis, ascariasis and ancylostomiasis [9–11]. The most common causes of death are status epilepticus and sequelae of intracranial hypertension.

**DIAGNOSIS**

History of exposure in an endemic area, even 30 years or more previously, is important. In an endemic area, neurocysticercosis is the most common cause of epilepsy in young adults. Family and friends, as well as the patient might have a current infection with *T. solium*; faecal examination occasionally therefore reveals eggs. The entire body should be palpated for subcutaneous and intramuscular nodules.

Definitive diagnosis depends on histological examination of a cysticercal cyst, which if subcutaneous can be excised under local anaesthesia. A fluid-filled opaque bladder 1 to 70 mm in diameter contains a single, solid, white sphere (the scolex). A translucent membrane with a central 'milk spot' is characteristic; if alive, the parasite may evaginate its head and neck, or it may be induced to do so by immersion in hot saline [4].

Radiologically, the ‘hallmark’ of neurocysticercosis consists of multiple elliptiform intracranial calcifications; a central calcified scolex surrounded by a calcified cyst wall are pathognomonic [1, 9]. However, calcification does not usually occur until at least three years after infection and often very much later. In one study, intracranial calcification was found in 36 per cent of patients within 10 years of the presumed date of infection [3]; however, 97 per cent already had calcification in skeletal muscles. CT-scanning may reveal non-calcified cysts, and is the most valuable radiological procedure [6, 9, 10]. When present in the ventricles contrast-enhancement is usually necessary because cyst and cerebrospinal fluid absorption values are similar [1]. Angiography, isotope scanning, pneumoencephalography, ventriculography, electroencephalography, and myelography occasionally yield abnormal results but have largely been replaced by CT-scanning [9, 14]. Although an eosinophilia with or without an overall leucocytosis [6, 9, 10] is sometimes present, this is of little or no value diagnostically. The finding of *T. solium* eggs in a faecal specimen is overall unusual [10]. Cerebrospinal fluid (CSF) pressure is occasionally elevated in neurocysticercosis [9]. Pleocytosis of 5 to 500 cells or more, with either a lymphocyte or eosinophil predominance can occur but is inconstant [1, 6, 9, 10]. Protein changes are non-specific; total protein and IgG may be elevated [1, 9]. A very low glucose concentration apparently carries a bad prognosis [6, 10]. Surgical biopsy is sometimes necessary for a definitive diagnosis [9].

Immunodiagnosis has recently improved; although formerly unreliable [4, 15] it is becoming increasingly sensitive and specific. Cross-reactions with hydatidosis, *Coenurus cerebralis*, and other tapeworms occasionally prove troublesome. Antigens from *C. cellulosae*, *C. bovis*, and adult tapeworms (*T. solium* and *T. saginata*) have all been used. Limited evidence suggests that
Neurocysticercosis antigen derived from cysticercal fluid possesses far greater reactivity than that from the cyst wall (see below). An indirect haemagglutination test has proved useful, but negative results certainly do not rule out active infection [8, 9, 16, 17]. An ELISA with sensitivity which varied between 61 and 79 per cent was recorded in 1982 [15, 18]; however, cross-reaction with hydatid and schistosomal infections and possibly angiostrongyliasis proved troublesome. A good deal of work has more recently been carried out using an ELISA incorporating C. cellulosae (and in some cases T. solium) antigen, on both serum and CSF specimens, with generally good results. Whilst a group in Mexico considered in 1986 that serological tests for neurocysticercosis still lacked reliability [19], this conclusion can no longer be widely upheld. Experiences of serum and CSF testing using an ELISA designed to detect IgG antibodies against C. cellulosae and T. solium antigens have been reported from Colombia [20], Mexico [21–23], and Durban, South Africa [24]. In the Colombia report, 89 and 93 per cent sensitivity and specificity rates, respectively, for detection of serum IgG antibodies against cysticercal antigen were achieved. In Mexico, comparable figures (87 and 90 per cent) were reported for serum testing, with sensitivity of 87 per cent and 100 per cent specificity for CSF specimens [21]; significantly higher sensitivity using both serum and CSF testing was reported in those whose disease ran a 'malignant' course \( p<0.01 \). In another study from Mexico, 85 and 90 per cent sensitivity rates in serum and CSF, respectively, were recorded with specificity approaching 100 per cent [22]; humoral responses did not correlate significantly with the clinical and laboratory findings; IgM, IgA and IgE were detected less often. The dot ELISA-linked and the standard ELISA (for detection of C. cellulosae antigen) have been compared using CSF specimens from 48 cases of neurocysticercosis; although both gave 100 per cent specificity, sensitivity rates were only 59 and 77 per cent, respectively [23]. Examination of both serum and CSF from the same individual has been advocated [24]; when both specimens were analysed, 87 per cent of 212 patients with neurocysticercosis could be diagnosed serologically, but when using CSF alone this rate fell to 67 per cent. Using an ELISA incorporating any one of three monoclonal antibodies generated from mice immunized with C. cellulosae scolex protein antigen, 100 per cent positivity was reported on serum samples in a study from Sao Paulo, Brazil [25]. Hybridoma-derived reagents for use with larval cestodes might also prove valuable in the future [4].

MANAGEMENT: CHEMOTHERAPY VERSUS SURGERY

Until 1979 the only form of treatment for this disease was surgical [17]. Since then chemotherapy has produced generally encouraging results. Experimental work using electron microscopy demonstrated that praziquantel can destroy the tegument along the whole pseudostrobila and the scolex of the related species C. fasciolaris [26]; furthermore using \(^{14}\)C-praziquantel, penetration of the cyst wall with death of the cysticercus within the cyst was apparent. Early clinical trials using this agent in cysticercosis were carried out in Mexico, Colombia, Chile, Brazil and South Korea [27]; dosage varied from 5–10 to 75 mg/kg daily, with total doses ranging from 45–60 to 1050 mg/kg. Satisfactory results were reported in 172 out of 192 cases of neurocysticercosis. Whether corticosteroids should be given also was unclear from these early studies. In a study in Colombia, 31 cases of neurocysticercosis (14 had previously undergone surgery) were treated with praziquantel combined with prednisone [17]; only one patient died, and this contrasted with a 50–80 per cent fatality rate in a group of 'historical' controls observed at the same institution. In another early assessment, 20 of 40 cases of the disease treated at São Paulo received dexamethasone in addition to praziquantel [28]; the authors concluded that by reducing inflammatory phenomena 'the administration of corticosteroids alongside praziquantel is highly indicated'.

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There were several subsequent reports of either single or very small numbers of cases [11, 29–34] and although most results were overall encouraging they are difficult to evaluate definitively. No large randomized double-blind trials are available. Assessment of the efficacy of chemotherapy can be evaluated by CT-scanning [10] in conjunction with serial measurement of serum antibody titres against cysticercal antigen [17, 27, 30]. Praziquantel is not without side-effects however. The most frequent problem has been the CSF reaction syndrome; this is characterized by fever, headache, meningismus, and exacerbation of many of the neurological symptoms. It is considered to be caused by an inflammatory reaction to dead and dying larvae, possibly analogous to the Jarisch–Herxheimer reaction [11]. Simultaneous administration of corticosteroids has produced encouraging results in preventing or attenuating this reaction [28, 29, 31].

The first large series of cases to be treated with praziquantel without a corticosteroid 'cover' was published from Mexico in 1984 [35]. Twenty-six patients were treated with 50 mg praziquantel/kg body-weight daily for 15 days; after three months all had improved clinically and 13 were asymptomatic. Furthermore, the total number of cysts, which was 152 at the beginning of treatment, had reduced to 51 with a reduction in mean diameter by 72 per cent; CT scans showed improvement in 25 cases and total remission of cysts in nine. An inflammatory reaction was common however (and affected 92 per cent); both protein and cell concentrations in CSF increased during treatment. In 17 untreated 'historical' controls followed for a mean of nine months, CT-scans showed either no change or worsening of disease. A further large group of 141 patients with neurocysticercosis treated with praziquantel 50 mg/kg daily (approximately half of them also received prednisone 30 mg daily) has been recorded [36]; 75 of them were subsequently considered cured (they were asymptomatic after five years and their cysts or nodules had either disappeared or had become calcified), while 35 showed both clinical and radiological improvement. However, intraventricular cysts in five of them had to be removed surgically (being unaffected by praziquantel), and 31 were unchanged or actually worsened. Failure of intraventricular cysts to improve was considered to be due to an inadequate concentration of praziquantel in the CSF.

An attempt has recently been made, from experience obtained in treating 40 patients, to delineate the indications for use of praziquantel (50 mg/kg daily for 15 days, and in severe cases 30 days) in neurocysticercosis [37]; these workers concluded that the groups which should be treated with this chemotherapeutic agent are those with: (i) active cerebral cysticercosis with cysts in the brain parenchyma or subarachnoid space; (ii) cysts in brain parenchyma, subarachnoid space and the ventricular system; and (iii) miliary cysticercosis, in which many cysts will be too small to be detected by CT-scanning. Those with cysts solely within the ventricular system should however be treated surgically, and not with praziquantel; group (ii) patients might also require surgery later. Although still a controversial matter, most physicians now strongly favour the addition of a corticosteroid cover to reduce the incidence of the CSF reaction syndrome [11, 38–41]; either dexamethasone or prednisone should be given before and during praziquantel treatment. One group of physicians considers that praziquantel administration without corticosteroids 'becomes increasingly hazardous with progressively severe (and advanced) cases of neurocysticercosis' [38]. Recommended dosage is 30–40 mg prednisone, or 12–16 mg dexamethasone daily [39–41].

Recently, albendazole (15 mg/kg body-weight daily for one month) has been used in seven patients (two had previously shown partial response to praziquantel) with neurocysticercosis [42]; at the beginning of treatment, 157 cysts were delineated by CT-scanning and at three months after treatment the number was 22, i.e. a reduction of 86 per cent. In the two patients who had previously received praziquantel, there was a response of 100 and 77 per cent respectively to albendazole. This early evidence is impressive but much larger numbers are
obviously required before a valid conclusion can be drawn. Limited use of flubendazole (another benzimidazole compound) has also been reported [6]. A further potentially useful chemotherapeutic agent is metriphonate [43]; 93 patients suffering from neurocysticercosis received 7.5 mg/kg body-weight daily for five consecutive days. Assessment by CT-scanning and immunological response indicated a satisfactory outcome at between six months and 10 years in approximately 80 per cent of patients. Here too, further evidence from large (preferably controlled) studies is required.

In certain situations, especially when CSF pressure is significantly raised, surgery is still the major line of treatment [1, 6, 8–10, 36, 44]; this applies to several groups. Cases in which intracranial hypertension is associated with intraventricular cysts and hydrocephalus, and where cysticerci are localized to the chiasma with an inflammatory reaction and adhesive arachnoiditis, fall into this category [44]. Removal of intraventricular (especially when freely mobile) or spinal cysts may also require intervention [6]. Treatment with high-dose corticosteroids is probably indicated before chemotherapy in patients with spinal cord involvement. Surgery also continues to be important in the treatment of cysts which do not respond to chemotherapy [36, 37]. Ventricular, ventriculo-peritoneal or other types of shunting are occasionally required [9].

CONTROL

Prophylaxis (and control) centres on improved public health measures. Man is the sole definitive host; therefore health education is of paramount importance [1]; indiscriminate human defaecation must be strongly discouraged and sewage should be treated to kill *T. solium* eggs. Husbandry practices must also be improved so that pigs do not wander widely and consume human faeces. The source of human infection with adult *T. solium* is infected pork; cysticerci in meat can be killed by freezing at −20°C for 12 h, or by cooking at 50°C. Careful inspection of pork is obviously of value. Whenever a *T. solium* infection is diagnosed in man, it should be treated with the appropriate anti-parasite agent(s); furthermore, family members and close contacts should be investigated for the presence of a *T. solium* infection, and treated accordingly.

In Mexico, antibodies which might be protective are present in the serum of up to 50 per cent of affected individuals [45]. This suggests that human vaccination might theoretically be possible in high-risk areas. Therefore, in areas with a high incidence rate of neurocysticercosis, where rearing of pigs is still uncontrolled in rural areas, and human defaecation remains indiscriminate, this possibility is worthy of serious consideration [46].

CONCLUSIONS

Neurocysticercosis remains a major worldwide health problem and accounts for numerous neurological presentations and admissions. An especially high index of suspicion for this disease is required when dealing with neurological problems in individuals who have lived in or visited areas where the disease is common. When *C. cellulosae* (preferably fluid) antigen [47] is available, serological testing (using an ELISA) is now both sensitive and specific in the diagnosis of active neurocysticercosis. Treatment has been revolutionized by the advent of effective chemotherapy; praziquantel (50 mg/kg daily for 15 days) has been shown to be of overall value (placebo-controlled trials would not now be ethically justified), but albendazole and metriphonate have not been adequately evaluated. When epilepsy persists after a full course of chemotherapy, a second course given up to six months after the first often achieves success. There can now be no doubt that a corticosteroid 'cover' should be added to any chemotherapeutic regimen for active neurocysticercosis. Nevertheless, surgery is still indicated.
in certain situations, especially when the ventricular system is affected, and intracranial hypertension is present. Prognosis has improved substantially since the introduction of chemotherapy; long-term anti-epileptic agents are now rarely necessary. Complications of surgical procedures (including shunting) such as meningitis, are now unusual [9], but disease of the ventricular system must always be viewed seriously [6, 10, 44]. Extirpation of basilar cysticerci [10] still carries a significant mortality rate.

REFERENCES


